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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07H 21/04, C07K 14/705, C12N 15/09, 15/63, C12Q 1/68 | A1

(11) International Publication Number: WO 99/43696

(43) International Publication Date: 2 September 1999 (02.09.99)

(21) International Application Number: PCT/US99/03826

(22) International Filing Date: 22 February 1999 (22.02.99)

(30) Priority Data:

60/076,687	25 February 1998 (25.02.98)	US
60/095,836	7 August 1998 (07.08.98)	US
60/116,448	19 January 1999 (19.01.99)	US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: HUMAN POTASSIUM CHANNEL GENES

(57) Abstract

Methods for isolating *K+Hnov* genes are provided. The *K+Hnov* nucleic acid compositions find use in identifying homologous or related proteins and the DNA sequences encoding such proteins; in producing compositions that modulate the expression or function of the protein; and in studying associated physiological pathways. In addition, modulation of the gene activity *in vivo* is used for prophylactic and therapeutic purposes, such as identification of cell type based on expression, and the like.

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HUMAN POTASSIUM CHANNEL GENES

INTRODUCTION

Background

Ion channels are multi-subunit, membrane bound proteins critical for maintenance of cellular homeostasis in nearly all cell types. Channels are involved in a myriad of processes including modulation of action potentials, regulation of cardiac myocyte excitability, heart rate, vascular tone, neuronal signaling, activation and proliferation of T-cells, and insulin secretion from pancreatic islet cells. In humans, ion channels comprise extended gene families with hundreds, or perhaps thousands, of both closely related and highly divergent family members. The majority of known channels regulate the passage of sodium (Na^+), chloride (Cl^-), calcium (Ca^{++}) and potassium (K^+) ions across the cellular membrane.

Given their importance in maintaining normal cellular physiology, it is not surprising that ion channels have been shown to play a role in heritable human disease. Indeed, ion channel defects are involved in predisposition to epilepsy, cardiac arrhythmia (long QT syndrome), hypertension (Bartter's syndrome), cystic fibrosis, (defects in the CFTR chloride channel), several skeletal muscle disorders (hyperkalemic periodic paralysis, paramyotonia congenita, episodic ataxia) and congenital neural deafness (Jervell-Lange-Nielson syndrome), amongst others.

The potassium channel gene family is believed to be the largest and most diverse ion channel family. K^+ channels have critical roles in multiple cell types andpathways, and are the focus of significant investigation. Four human conditions, episodic ataxia with myokymia, long QT syndrome, epilepsy and Bartter's syndrome have been shown to be caused by defective K^+ ion channels. As the K^+ channel family is very diverse, and given that these proteins are critical components of virtually all cells, it is likely that abnormal K^+ channels will be involved in the etiology of additional renal, cardiovascular and central nervous system disorders of interest to the medical and pharmaceutical community.

The K^+ channel superfamily can be broadly classified into groups, based upon the number of transmembrane domain (TMD) segments in the mature

protein. The minK (IsK) gene contains a single TMD, and although not a channel by itself, minK associates with different K^+ channel subunits, such as KvLQT1 and HERG to modify the activity of these channels. The inward rectifying K+ channels (GIRK, IRK, CIR, ROMK) contain 2 TMD domains and a highly conserved pore domain. Twik-1 is a member of the newly emerging 4TMD K^+ channel subset. Twik-like channels (leak channels) are involved in maintaining the steady-state K^+ potentials across membranes and therefore the resting potential of the cell near the equilibrium potential for potassium (Duprat *et al.* (1997) EMBO J **16**(17):5464-5471). These proteins are particularly intriguing targets for therapeutic regulation. The 6TMD, or Shaker-like channels, presently comprise the largest subset of known K^+ channels. The slopoke (slo) related channels, or Ca^{++} regulated channels apparently have either 10 TMD, or 6 TMD with 4 additional hydrophobic domains.

Four transmembrane domain, tandem pore domain K+ channels (4T/2P channels) represent a new family of potassium selective ion channels involved in the control of background membrane conductances. In mammals, five channels fitting the 4T/2P architecture have been described: TWIK, TREK, TASK-1, TASK-2 and TRAAK. The 4T/2P channels all have distinct characteristics, but are all thought to be involved in maintaining the steady-state K^+ potentials across membranes and therefore the resting potential of the cell near the equilibrium potential for potassium (Duprat *et al.* (1997) EMBO J **16**(17):5464-5471). These proteins are particularly intriguing targets for therapeutic regulation. Within this group, TWIK-1, TREK-1 and TASK-1 and TASK-2 are widely distributed in many different tissues, while TRAAK is present exclusively in brain, spinal cord and retina. The 4T/2P channels have different physiologic properties; TREK-1 channels, are outwardly rectifying (Fink *et al.* (1996) EMBO J **15**(24):6854-62), while TWIK-1 channels, are inwardly rectifying (Lesage *et al.* (1996) EMBO J **15**(5):1004-11. TASK channels are regulated by changes in PH while TRAAK channels are stimulated by arachidonic acid (Reyes *et al.* (1998) JBC **273**(47):30863-30869).

The degree of sequence homology between different K^+ channel genes is substantial. At the amino acid level, there is about 40% similarity between

different human genes, with distinct regions having higher homology, specifically the pore domain. It has been estimated that the K+ channel gene family contains approximately 10^2-10^3 individual genes. Despite the large number of potential genes, an analysis of public sequence databases and the scientific literature demonstrates that only a small number, approximately 20-30, have been identified. This analysis suggests that many of these important genes remain to be identified.

Potassium channels are involved in multiple different processes and are important regulators of homeostasis in nearly all cell types. Their relevance to basic cellular physiology and role in many human diseases suggests that pharmacological agents could be designed to specific channel subtypes and these compounds then applied to a large market (Bulman, D.E. (1997) Hum Mol Genet **6**:1679-1685; Ackerman, M.J. and Clapham D.E. (1997) NEJM **336**:1575-1586, Curran, M.E. (1998) Current Opinion in Biotechnology **9**:565-572). The variety of therapeutic agents that modulate K+ channel activity reflects the diversity of physiological roles and importance of K+ channels in cellular function. A difficulty encountered in therapeutic use of therapeutic agents that modify K+ channel activity is that the presently available compounds tend to be non-specific and elicit both positive and negative responses, thereby reducing clinical efficacy. To facilitate development of specific compounds it is desirable to have further characterize novel K+ channels for use in *in vitro* and *in vivo* assays.

Relevant Literature

A large body of literature exists in the general area of potassium channels. A review of the literature may be found in the series of books, "The Ion Channel Factsbook", volumes 1-4, by Edward C. Conley and William J. Brammar, Academic Press. An overview is provided of: extracellular ligand-gated ion channels (ISBN: 0121844501), intracellular ligand-gated channels (ISBN: 012184451X), Inward rectifier and intercellular channels (ISBN: 0121844528), and voltage gated channels (ISBN: 0121844536). Hille, B. (1992) "Ionic Channels of Excitable Membranes", 2nd Ed. Sunderland MA:Sinauer Associates, also reviews potassium channels.

Jan and Jan (1997) Annu. Rev. Neurosci. **20**:91-123 review cloned potassium channels from eukaryotes and prokaryotes. Ackerman and Clapham (1997) N. Engl. J. Med. **336**:1575-1586 discuss the basic science of ion channels in connection with clinical disease. Bulman (1997) Hum. Mol. Genet. **6**:1679-1685 describe some phenotypic variation in ion channel disorders.

Stephan *et al.* (1994) Neurology **44**:1915-1920 describe a pedigree segregating a myotonia with muscular hypertrophy and hyperirritability as an autosomal dominant trait (rippling muscle disease, Ricker *et al.* (1989) Arch. Neurol. 46405-408). Electromyography demonstrated that mechanical stimulation provoked electrically silent contractions. The responsible gene was localized to the distal end of the long arm of chromosome 1, in a 12-cM region near D1S235.

Type II pseudohypoaldosteronism is the designation used for a syndrome of chronic mineralocorticoid-resistant hyperkalemia with hypertension. The primary abnormality in type II PHA is thought to be a specific defect of the renal secretory mechanism for potassium, which limits the kaliuretic response to, but not the sodium and chloride reabsorptive effect of, mineralocorticoid. By analysis of linkage in families with autosomal dominant transmission, Mansfield *et al.* (1997) Nature Genet. **16**:202-205 demonstrated locus heterogeneity of the trait, with linkage of the PHA2 gene to 1q31-q42 and 17p11-q21.

Sequences of four transmembrane, two pore potassium channels have been previously described. Reyes *et al.* (1998) J Biol Chem **273**(47):30863-30869 discloses a pH sensitive channel. As with the related TASK-1 and TRAAK channels, the outward rectification is lost at high external K+ concentration. The TRAAK channel is described by Fink *et al.* (1998) EMBO J **17**(12):3297-308. A cardiac two-pore channel is described in Kim *et al.* (1998) Circ Res **82**(4):513-8. An open rectifier potassium channel with two pore domains in tandem and having a postsynaptic density protein binding sequence at the C terminal was cloned by Leonoudakis *et al.* (1998) J Neurosci **18**(3):868-77.

The electrophysiological properties of Task channels are of interest, (Duprat *et al.* (1997) EMBO J **16**:5464-71). TASK currents are K+-selective, instantaneous and non-inactivating. They show an outward rectification when external [K+] is low, which is not observed for high [K+]out, suggesting a lack of

intrinsic voltage sensitivity. The absence of activation and inactivation kinetics as well as voltage independence are characteristic of conductances referred to as leak or background conductances. TASK is very sensitive to variations of extracellular pH in a narrow physiological range, a property probably essential for its physiological function, and suggests that small pH variations may serve a communication role in the nervous system.

SUMMARY OF THE INVENTION

Isolated nucleotide compositions and sequences are provided for *K+Hnov* genes. The *K+Hnov* nucleic acid compositions find use in identifying homologous or related genes; in producing compositions that modulate the expression or function of its encoded proteins; for gene therapy; mapping functional regions of the proteins; and in studying associated physiological pathways. In addition, modulation of the gene activity *in vivo* is used for prophylactic and therapeutic purposes, such as treatment of potassium channel defects, identification of cell type based on expression, and the like.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

Nucleic acid compositions encoding *K+Hnov* polypeptides are provided. They are used in identifying homologous or related genes; in producing compositions that modulate the expression or function of the encoded proteins; for gene therapy; mapping functional regions of the proteins; and in studying associated physiological pathways. The *K+Hnov* gene products are members of the potassium channel gene family, and have high degrees of homology to known potassium channels. The encoded polypeptides may be alpha subunits, which form the functional channel, or accessory subunits that act to modulate the channel activity.

CHARACTERIZATION OF *K+HNOV*

The sequence data predict that the provided *K+Hnov* genes encode potassium channels. Table 1 summarizes the DNA sequences, corresponding SEQ ID NOs, chromosomal locations, and polymorphisms. The provided

sequences may encode a predicted K+channel, *e.g.* voltage gated, inward rectifier, *etc.*; or a modulatory subunit.

Electrophysiologic characterization of ion channels is an important part of understanding channel function. Full length ion channel cDNAs may be combined with proper vectors to form expression constructs of each individual channel. Functional analyses of expressed channels can be performed in heterologous systems, or by expression in mammalian cell lines. For expression analyses in heterologous systems such as *Xenopus* oocytes, synthetic mRNA is made through *in vitro* transcription of each channel construct. mRNA is then injected, singly or in combination with interacting channel subunit mRNAs, into prepared oocytes and the cells allowed to express the channel for several days. Oocytes expressing the channel of interest are then analyzed by whole cell voltage clamp and patch clamp techniques.

To determine the properties of each channel when expressed in mammalian cells expression vectors specific to this type of analyses may be constructed and the resultant construct used to transform the target cells (for example human embryonic kidney (HEK) cells). Both stable and transiently expressing lines may be studied using whole cell voltage clamp and patch clamp techniques. Data obtained from EP studies includes, but is not limited to: current profiles elicited by depolarization and hyperpolarization, current-voltage (I-V) relationships, voltage dependence of activation, biophysical kinetics of channel activation, deactivation, and inactivation, reversal potential, ion selectivity, gating properties and sensitivity to channel antagonists and agonists.

Heterologous or mammalian cell lines expressing the novel channels can be used to characterize small molecules and drugs which interact with the channel. The same experiments can be used to assay for novel compounds which interact with the expressed channels.

In many cases the functional ion channel formed by K+Hnov polypeptides will be heteromultimers. Heteromultimers are known to form between different voltage gated, outward rectifying potassium channel α subunits, generally comprising four subunits, and frequently associated with auxiliary, β subunits. Typically such α subunits share a six-transmembrane domain structure (S1-S6),

with one highly positively charged domain (S4) and a pore region situated between S5 and S6. Examples of such subunits are K+Hnov4, K+Hnov9, and K+Hnov12. Channels are also formed by mutimerization of subunits of the two transmembrane and one pore architecture. It is predicted that two subunits of K+Hnov49 or K+Hnov59 will be required to form a functional channel.

Heteromultimers of greatest interest are those that form between subunits expressed in the same tissues, and are a combination of subunits from the same species. In addition, the formation of multimers between the subject polypeptides and subunits that form functional channels are of particular interest. The resulting channel may have decreased or increased conductance relative to a homomultimer, and may be altered in response to beta subunits or other modulatory molecules.

Known voltage gated K+ channel α subunits include Kv1.1-1.8 (Gutman *et al.* (1993) Sem. Neurosci. 5:101-106); Kv2.1-2.2; Kv3.1-3.4; Kv4.1-4.3; Kv5.1; Kv6.1; Kv7.1; Kv8.1; Kv9.1-9.2. The subunits capable of forming ion inducing channels include all of those in the Kv1 through Kv4; and Kv7 families. The Kv5.1, Kv6.1, Kv8.1 and Kv9.1-9.2 subunits may be electrically silent, but functional in modifying the properties in heteromultimers.

TABLE 1

Name	cDNA SEQ	Protein SEQ	Polymorphisms	Chromosome Position	Channel Type
K+Hnov1	SEQ ID NO:1	SEQ ID NO:2	Alternative poly(A) tail: 1236, 2395	2q37	ATP-sensitive inward rectifying
K+Hnov4	SEQ ID NO:3	SEQ ID NO:4	A312C T335C A377G T344C A401G CA410-411GG (Ala/Thr)	unknown	Voltage gated K+ channel
K+Hnov6	SEQ ID NO:5	SEQ ID NO:6		2p23	Delayed rectifying K+ channel
K+Hnov9	SEQ ID NO:7	SEQ ID NO:8	Alternative poly(A) tail: 2304	8q23	Voltage gated K+ channel
K+Hnov12	SEQ ID NO:9	SEQ ID NO:10	C321T (Pro/Leu) A375G (Glu/Gly) C407T (Leu/Phe)	Xp21	Voltage gated K+ channel
K+Hnov15	SEQ ID NO:11	SEQ ID NO:12	Alternative poly(A) tail: 1427 A689G (Gly/Arg)	13q14	modulatory subunit
K+Hnov27	SEQ ID NO:13	SEQ ID NO:14	T365A (Ile/Asn)	18q12	modulatory subunit
K+Hnov2	SEQ ID NO:15	SEQ ID NO:16	N/A	N/A	4 transmembrane domain, 2 pore domain K+ channel

K+Hnov 11	SEQ ID NO:17	SEQ ID NO:18	N/A	N/A	Human ortholog of murine gene, 6 transmembrane dominas, voltage gated, delayed rectifier K+ channel
K+Hnov 14	SEQ ID NO:19	SEQ ID NO:20	C3168T	12q14	6 transmembrane domain, voltage gated K+ channel
K+Hnov28	SEQ ID NO:21-24	SEQ ID NO:25	4 alternative 5' splices	3q29	Modulatory subunit
K+Hnov42	SEQ ID NO:26	SEQ ID NO:27	G1162A; T1460A; T2496A	8q11	Homology to K+ channel protein of *C. elegans*
K+Hnov44	SEQ ID NO:28-29	SEQ ID NO:30	N/A	22p13	beta-subunit
K'Hnov49	SEQ ID NO:80	SEQ ID NO:81	$(ATCT)_n$ repeats in the 3' UTR sequence, starting at position 2166	1q41	4T/2P channel; linked to the disease loci for rippling muscle disease 1 (RMD1), and type II pseudohypoaldosteronism
K'Hnov59	SEQ ID NO:82	SEQ ID NO:83	N/A	chr19	4T/2P channel

K+HNOV NUCLEIC ACID COMPOSITIONS

As used herein, the term "K+Hnov" is generically used to refer to any one of the provided genetic sequences listed in Table 1. Where a specific K+Hnov sequence is intended, the numerical designation, *e.g.* K49 or K59, will be added. Nucleic acids encoding *K+Hnov* potassium channels may be cDNA or genomic DNA or a fragment thereof. The term "*K+Hnov* gene" shall be intended to mean the open reading frame encoding any of the provided *K+Hnov* polypeptides, introns, as well as adjacent 5' and 3' non-coding nucleotide sequences involved in the regulation of expression, up to about 20 kb beyond the coding region, but possibly further in either direction. The gene may be introduced into an appropriate vector for extrachromosomal maintenance or for integration into a host genome.

The term "cDNA" as used herein is intended to include all nucleic acids that share the arrangement of sequence elements found in native mature mRNA species, where sequence elements are exons and 3' and 5' non-coding regions. Normally mRNA species have contiguous exons, with the intervening introns, when present, removed by nuclear RNA splicing, to create a continuous open reading frame encoding a K+Hnov protein.

A genomic sequence of interest comprises the nucleic acid present between the initiation codon and the stop codon, as defined in the listed sequences, including all of the introns that are normally present in a native chromosome. It may further include the 3' and 5' untranslated regions found in the mature mRNA. It may further include specific transcriptional and translational regulatory sequences, such as promoters, enhancers, *etc.*, including about 1 kb, but possibly more, of flanking genomic DNA at either the 5' or 3' end of the transcribed region. The genomic DNA may be isolated as a fragment of 100 kbp or smaller; and substantially free of flanking chromosomal sequence. The genomic DNA flanking the coding region, either 3' or 5', or internal regulatory sequences as sometimes found in introns, contains sequences required for proper tissue and stage specific expression.

The sequence of the 5' flanking region may be utilized for promoter elements, including enhancer binding sites, that provide for developmental regulation in tissues where *K+Hnov* genes are expressed. The tissue specific expression is useful for determining the pattern of expression, and for providing promoters that mimic the native pattern of expression. Naturally occurring polymorphisms in the promoter regions are useful for determining natural variations in expression, particularly those that may be associated with disease.

Alternatively, mutations may be introduced into the promoter regions to determine the effect of altering expression in experimentally defined systems. Methods for the identification of specific DNA motifs involved in the binding of transcriptional factors are known in the art, *e.g.* sequence similarity to known binding motifs, gel retardation studies, *etc.* For examples, see Blackwell *et al.* (1995) Mol Med **1**: 194-205; Mortlock *et al.* (1996) Genome Res. **6**: 327-33; and Joulin and Richard-Foy (1995) Eur J Biochem **232**: 620-626.

The regulatory sequences may be used to identify *cis* acting sequences required for transcriptional or translational regulation of *K+Hnov* expression, especially in different tissues or stages of development, and to identify *cis* acting sequences and *trans* acting factors that regulate or mediate *K+Hnov* expression. Such transcription or translational control regions may be operably linked to a *K+Hnov* gene in order to promote expression of wild type or altered *K+Hnov* or other proteins of interest in cultured cells, or in embryonic, fetal or adult tissues, and for gene therapy.

The nucleic acid compositions of the subject invention may encode all or a part of the subject polypeptides. Double or single stranded fragments may be obtained of the DNA sequence by chemically synthesizing oligonucleotides in accordance with conventional methods, by restriction enzyme digestion, by PCR amplification, *etc.* For the most part, DNA fragments will be of at least 15 nt, usually at least 18 nt or 25 nt, and may be at least about 50 nt. Such small DNA fragments are useful as primers for PCR, hybridization screening probes, *etc.* Larger DNA fragments, *i.e.* greater than 100 nt are useful for production of the encoded polypeptide. For use in amplification reactions, such as PCR, a pair of

primers will be used. The exact composition of the primer sequences is not critical to the invention, but for most applications the primers will hybridize to the subject sequence under stringent conditions, as known in the art. It is preferable to choose a pair of primers that will generate an amplification product of at least about 50 nt, preferably at least about 100 nt. Algorithms for the selection of primer sequences are generally known, and are available in commercial software packages. Amplification primers hybridize to complementary strands of DNA, and will prime towards each other.

The *K+Hnov* genes are isolated and obtained in substantial purity, generally as other than an intact chromosome. Usually, the DNA will be obtained substantially free of other nucleic acid sequences that do not include a *K+Hnov* sequence or fragment thereof, generally being at least about 50%, usually at least about 90% pure and are typically "recombinant", *i.e.* flanked by one or more nucleotides with which it is not normally associated on a naturally occurring chromosome.

The DNA may also be used to identify expression of the gene in a biological specimen. The manner in which one probes cells for the presence of particular nucleotide sequences, as genomic DNA or RNA, is well established in the literature and does not require elaboration here. DNA or mRNA is isolated from a cell sample. The mRNA may be amplified by RT-PCR, using reverse transcriptase to form a complementary DNA strand, followed by polymerase chain reaction amplification using primers specific for the subject DNA sequences. Alternatively, the mRNA sample is separated by gel electrophoresis, transferred to a suitable support, *e.g.* nitrocellulose, nylon, *etc.*, and then probed with a fragment of the subject DNA as a probe. Other techniques, such as oligonucleotide ligation assays, *in situ* hybridizations, and hybridization to DNA probes arrayed on a solid chip may also find use. Detection of mRNA hybridizing to the subject sequence is indicative of *K+Hnov* gene expression in the sample.

The sequence of a *K+Hnov* gene, including flanking promoter regions and coding regions, may be mutated in various ways known in the art to generate targeted changes in promoter strength, sequence of the encoded protein, *etc.*

The DNA sequence or protein product of such a mutation will usually be substantially similar to the sequences provided herein, *i.e.* will differ by at least one nucleotide or amino acid, respectively, and may differ by at least two but not more than about ten nucleotides or amino acids. The sequence changes may be substitutions, insertions or deletions. Deletions may further include larger changes, such as deletions of a domain or exon. Other modifications of interest include epitope tagging, *e.g.* with the FLAG system, HA, *etc.* For studies of subcellular localization, fusion proteins with green fluorescent proteins (GFP) may be used.

Techniques for *in vitro* mutagenesis of cloned genes are known. Examples of protocols for site specific mutagenesis may be found in Gustin *et al.*, *Biotechniques* 14:22 (1993); Barany, *Gene* 37:111-23 (1985); Colicelli *et al.*, *Mol Gen Genet* 199:537-9 (1985); and Prentki *et al.*, *Gene* 29:303-13 (1984). Methods for site specific mutagenesis can be found in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, CSH Press 1989, pp. 15.3-15.108; Weiner *et al.*, *Gene* 126:35-41 (1993); Sayers *et al.*, *Biotechniques* 13:592-6 (1992); Jones and Winistorfer, *Biotechniques* 12:528-30 (1992); Barton *et al.*, *Nucleic Acids Res* 18:7349-55 (1990); Marotti and Tomich, *Gene Anal Tech* 6:67-70 (1989); and Zhu, *Anal Biochem* 177:120-4 (1989). Such mutated genes may be used to study structure-function relationships of *K+Hnov*, or to alter properties of the protein that affect its function or regulation.

Homologs and orthologs of K+Hnov genes are identified by any of a number of methods. A fragment of the provided cDNA may be used as a hybridization probe against a cDNA library from the target organism of interest, where low stringency conditions are used. The probe may be a large fragment, or one or more short degenerate primers. Nucleic acids having sequence similarity are detected by hybridization under low stringency conditions, for example, at 50°C and 6XSSC (0.9 M sodium chloride/0.09 M sodium citrate) and remain bound when subjected to washing at 55°C in 1XSSC (0.15 M sodium chloride/0.015 M sodium citrate). Sequence identity may be determined by hybridization under stringent conditions, for example, at 50°C or higher and

0.1XSSC (15 mM sodium chloride/01.5 mM sodium citrate). Nucleic acids having a region of substantial identity to the provided K+Hnov sequences, *e.g.* allelic variants, genetically altered versions of the gene, *etc.*, bind to the provided K+Hnov sequences under stringent hybridization conditions. By using probes, particularly labeled probes of DNA sequences, one can isolate homologous or related genes. The source of homologous genes may be any species, *e.g.* primate species, particularly human; rodents, such as rats and mice, canines, felines, bovines, ovines, equines, yeast, nematodes, *etc.*

Between mammalian species, *e.g.* human and mouse, homologs have substantial sequence similarity, *i.e.* at least 75% sequence identity between nucleotide sequences, in some cases 80 or 90% sequence identity, and may be as high as 95% sequence identity between closely related species. Sequence similarity is calculated based on a reference sequence, which may be a subset of a larger sequence, such as a conserved motif, coding region, flanking region, *etc.* A reference sequence will usually be at least about 18 nt long, more usually at least about 30 nt long, and may extend to the complete sequence that is being compared. Algorithms for sequence analysis are known in the art, such as BLAST, described in Altschul et al. (1990), J. Mol. Biol. 215:403-10. In general, variants of the invention have a sequence identity greater than at least about 65%, preferably at least about 75%, more preferably at least about 85%, and may be greater than at least about 90% or more as determined by the Smith-Waterman homology search algorithm as implemented in MPSRCH program (Oxford Molecular). Exemplary search parameters for use with the MPSRCH program in order to identify sequences of a desired sequence identity are as follows: gap open penalty: 12; and gap extension penalty: 1.

K+Hnov Polypeptides

The subject nucleic acid sequences may be employed for producing all or portions of K+Hnov polypeptides. For expression, an expression cassette may be employed. The expression vector will provide a transcriptional and translational initiation region, which may be inducible or constitutive, where the coding region

is operably linked under the transcriptional control of the transcriptional initiation region, and a transcriptional and translational termination region. These control regions may be native to a *K+Hnov* gene, or may be derived from exogenous sources.

The peptide may be expressed in prokaryotes or eukaryotes in accordance with conventional ways, depending upon the purpose for expression. For large scale production of the protein, a unicellular organism, such as *E. coli, B. subtilis, S. cerevisiae*, insect cells in combination with baculovirus vectors, or cells of a higher organism such as vertebrates, particularly mammals, *e.g.* COS 7 cells, may be used as the expression host cells. In some situations, it is desirable to express the *K+Hnov* gene in eukaryotic cells, where the K+Hnov protein will benefit from native folding and post-translational modifications. Small peptides can also be synthesized in the laboratory. Peptides that are subsets of the complete *K+Hnov* sequence may be used to identify and investigate parts of the protein important for function, or to raise antibodies directed against these regions.

Fragments of interest include the transmembrane and pore domains, the signal sequences, regions of interaction between subunits, *etc.* Such domains will usually include at least about 20 amino acids of the provided sequence, more usually at least about 50 amino acids, and may include 100 amino acids or more, up to the complete domain. Binding contacts may be comprised of non-contiguous sequences, which are brought into proximity by the tertiary structure of the protein. The sequence of such fragments may be modified through manipulation of the coding sequence, as described above. Truncations may be performed at the carboxy or amino terminus of the fragment, e.g. to determine the minimum sequence required for biological activity.

With the availability of the protein or fragments thereof in large amounts, by employing an expression host, the protein may be isolated and purified in accordance with conventional ways. A lysate may be prepared of the expression host and the lysate, purified using HPLC, exclusion chromatography, gel electrophoresis, affinity chromatography, or other purification technique. The

purified protein will generally be at least about 80% pure, preferably at least about 90% pure, and may be up to and including 100% pure. Pure is intended to mean free of other proteins, as well as cellular debris.

The expressed K+Hnov polypeptides are useful for the production of antibodies, where short fragments provide for antibodies specific for the particular polypeptide, and larger fragments or the entire protein allow for the production of antibodies over the surface of the polypeptide. Antibodies may be raised to the wild-type or variant forms of K+Hnov. Antibodies may be raised to isolated peptides corresponding to specific domains, *e.g.* the pore domain and the transmembrane domain, or to the native protein.

Antibodies are prepared in accordance with conventional ways, where the expressed polypeptide or protein is used as an immunogen, by itself or conjugated to known immunogenic carriers, *e.g.* KLH, pre-S HBsAg, other viral or eukaryotic proteins, or the like. Various adjuvants may be employed, with a series of injections, as appropriate. For monoclonal antibodies, after one or more booster injections, the spleen is isolated, the lymphocytes immortalized by cell fusion, and then screened for high affinity antibody binding. The immortalized cells, *i.e.* hybridomas, producing the desired antibodies may then be expanded. For further description, see <u>Monoclonal Antibodies: A Laboratory Manual</u>, Harlow and Lane eds., Cold Spring Harbor Laboratories, Cold Spring Harbor, New York, 1988. If desired, the mRNA encoding the heavy and light chains may be isolated and mutagenized by cloning in *E. coli*, and the heavy and light chains mixed to further enhance the affinity of the antibody. Alternatives to *in vivo* immunization as a method of raising antibodies include binding to phage "display" libraries, usually in conjunction with *in vitro* affinity maturation.

K+HNOV GENOTYPING

The subject nucleic acid and/or polypeptide compositions may be used to genotyping and other analysis for the presence of polymorphisms in the sequence, or variation in the expression of the subject genes. Genotyping may be performed to determine whether a particular polymorphisms is associated with

a disease state or genetic predisposition to a disease state, particularly diseases associated with defects in excitatory properties of cells, *e.g.* cardiac, muscle, renal and neural cells. Disease of interest include rippling muscle disease, and type II psuedohypoaldosteronism.

Clinical disorders associated with K+ channel defects include long-QT syndrome; a congenital disorder affecting 1 in 10,000-15,000. Affected individuals have a prolonged QT interval in the electrocardiogram due to a delayed repolarization of the ventricle. Genetic linkage analyses identified two loci for long QT syndrome, LQT1, in 11p15.5 and LQT2, in 7q35-36. Positional cloning techniques identified the novel K+ channel KvLQT1 on chromosome 11 while candidate gene analysis identified causative mutations in the HERG K+ channel for LQT2.

The weaver mouse exhibits several abnormal neurological symptoms, including severe ataxia, loss of granule cell neurons in the cerebellum and dopaminergic cells in the substantia nigra, as well as seizures and male infertility. A G-protein-coupled K+ channel having a mutation in the conserved pore domain has been determined to cause the disease. The pancreatic-islet ß-cell ATP-sensitive K+ channel (KATP) is composed of two subunits, the sulfonylurea receptor (SUR) and the inward rectifier K+ channel Kir6.2. Mutations in both SUR and Kir6.2 have been identified in patients with persistent hyperinsulinemic hypoglycemia of infancy, which is caused by unregulated secretion of insulin.

Genotyping may also be performed for pharmacogenetic analysis to assess the association between an individual's genotype and that individual's ability to react to a therapeutic agent. Differences in target sensitivity can lead to toxicity or therapeutic failure. Relationships between polymorphisms in channel expression or specificity can be used to optimize therapeutic dose administration.

Genetic polymorphisms are identified in the K+Hnov gene (examples are listed in table 1), *e.g.* the repeat variation in the 3' UTR of K49. Nucleic acids comprising the polymorphic sequences are used to screen patients for altered reactivity and adverse side effects in response to drugs that act on K+ channels.

K+Hnov genotyping is performed by DNA or RNA sequence and/or hybridization analysis of any convenient sample from a patient, *e.g.* biopsy material, blood sample, scrapings from cheek, etc. A nucleic acid sample from an individual is analyzed for the presence of polymorphisms in K+Hnov, particularly those that affect the activity, responsiveness or expression of K+Hnov. Specific sequences of interest include any polymorphism that leads to changes in basal expression in one or more tissues, to changes in the modulation of K+Hnov expression, or alterations in K+Hnov specificity and/or activity.

The effect of a polymorphism in K+Hnov gene sequence on the response to a particular agent may be determined by *in vitro* or *in vivo* assays. Such assays may include monitoring during clinical trials, testing on genetically defined cell lines, etc. The response of an individual to the agent can then be predicted by determining the K+Hnov genotype with respect to the polymorphism. Where there is a differential distribution of a polymorphism by racial background, guidelines for drug administration can be generally tailored to a particular ethnic group.

Biochemical studies may be performed to determine whether a sequence polymorphism in a *K+Hnov* coding region or control regions is associated with disease, for example the association of K+Hnov 9 with idiopathic generalized epilepsy. Disease associated polymorphisms may include deletion or truncation of the gene, mutations that alter expression level, that affect the electrical activity of the channel, *etc.*

A number of methods are available for analyzing nucleic acids for the presence of a specific sequence. Where large amounts of DNA are available, genomic DNA is used directly. Alternatively, the region of interest is cloned into a suitable vector and grown in sufficient quantity for analysis. The nucleic acid may be amplified by conventional techniques, such as the polymerase chain reaction (PCR), to provide sufficient amounts for analysis. The use of the polymerase chain reaction is described in Saiki *et al.* (1985) Science **239**:487, and a review of current techniques may be found in Sambrook *et al.* Molecular Cloning: A Laboratory Manual, CSH Press 1989, pp.14.2-14.33. Amplification may be used

to determine whether a polymorphism is present, by using a primer that is specific for the polymorphism. Alternatively, various methods are known in the art that utilize oligonucleotide ligation as a means of detecting polymorphisms, for examples see Riley *et al.* (1990) N.A.R. **18**:2887-2890; and Delahunty *et al.* (1996) Am. J. Hum. Genet.**58**:1239-1246.

A detectable label may be included in an amplification reaction. Suitable labels include fluorochromes, e.g. fluorescein isothiocyanate (FITC), rhodamine, Texas Red, phycoerythrin, allophycocyanin, 6-carboxyfluorescein (6-FAM), 2',7'-dimethoxy-4',5'- dichloro-6-carboxyfluorescein (JOE), 6-carboxy-X-rhodamine (ROX), 6-carboxy-2',4',7',4,7- hexachlorofluorescein (HEX), 5-carboxyfluorescein (5-FAM) or N,N,N',N'-tetramethyl-6- carboxyrhodamine (TAMRA), radioactive labels, e.g. 32P, 35S, 3H; etc. The label may be a two stage system, where the amplified DNA is conjugated to biotin, haptens, etc. having a high affinity binding partner, e.g. avidin, specific antibodies, etc., where the binding partner is conjugated to a detectable label. The label may be conjugated to one or both of the primers. Alternatively, the pool of nucleotides used in the amplification is labeled, so as to incorporate the label into the amplification product.

The sample nucleic acid, *e.g.* amplified or cloned fragment, is analyzed by one of a number of methods known in the art. The nucleic acid may be sequenced by dideoxy or other methods. Hybridization with the variant sequence may also be used to determine its presence, by Southern blots, dot blots, *etc.* The hybridization pattern of a control and variant sequence to an array of oligonucleotide probes immobilised on a solid support, as described in U.S. 5,445,934, or in WO95/35505, may also be used as a means of detecting the presence of variant sequences. Single strand conformational polymorphism (SSCP) analysis, denaturing gradient gel electrophoresis (DGGE), mismatch cleavage detection, and heteroduplex analysis in gel matrices are used to detect conformational changes created by DNA sequence variation as alterations in electrophoretic mobility. Alternatively, where a polymorphism creates or destroys a recognition site for a restriction endonuclease (restriction fragment length polymorphism, RFLP), the sample is digested with that endonuclease, and the

products size fractionated to determine whether the fragment was digested. Fractionation is performed by gel or capillary electrophoresis, particularly acrylamide or agarose gels.

In one embodiment of the invention, an array of oligonucleotides are provided, where discrete positions on the array are complementary to one or more of the provided sequences, *e.g.* oligonucleotides of at least 12 nt, frequently 20 nt, or larger, and including the sequence flanking a polymorphic position in a K^+Hnov sequence; coding sequences for different K^+Hnov channels, panels of ion channels comprising one or more of the provided K^+ channels; *etc.* Such an array may comprise a series of oligonucleotides, each of which can specifically hybridize to a different polymorphism. For examples of arrays, see Hacia *et al.* (1996) Nature Genetics 14:441-447; Lockhart *et al.* (1996) Nature Biotechnol. 14:1675-1680; and De Risi *et al.* (1996) Nature Genetics 14:457-460.

Screening for polymorphisms in K+Hnov may be based on the functional or antigenic characteristics of the protein. Protein truncation assays are useful in detecting deletions that may affect the biological activity of the protein. Various immunoassays designed to detect polymorphisms in K+Hnov proteins may be used in screening. Where many diverse genetic mutations lead to a particular disease phenotype, functional protein assays have proven to be effective screening tools. The activity of the encoded K+Hnov protein as a potassium channel may be determined by comparison with the wild-type protein.

Antibodies specific for a K+Hnov may be used in staining or in immunoassays. Samples, as used herein, include biological fluids such as semen, blood, cerebrospinal fluid, tears, saliva, lymph, dialysis fluid and the like; organ or tissue culture derived fluids; and fluids extracted from physiological tissues. Also included in the term are derivatives and fractions of such fluids. The cells may be dissociated, in the case of solid tissues, or tissue sections may be analyzed. Alternatively a lysate of the cells may be prepared.

Diagnosis may be performed by a number of methods to determine the absence or presence or altered amounts of normal or abnormal K+Hnov polypeptides in patient cells. For example, detection may utilize staining of cells

or histological sections, performed in accordance with conventional methods. The antibodies of interest are added to the cell sample, and incubated for a period of time sufficient to allow binding to the epitope, usually at least about 10 minutes. The antibody may be labeled with radioisotopes, enzymes, fluorescers, chemiluminescers, or other labels for direct detection. Alternatively, a second stage antibody or reagent is used to amplify the signal. Such reagents are well known in the art. For example, the primary antibody may be conjugated to biotin, with horseradish peroxidase-conjugated avidin added as a second stage reagent. Alternatively, the secondary antibody conjugated to a flourescent compound, *e.g.* flourescein, rhodamine, Texas red, *etc.* Final detection uses a substrate that undergoes a color change in the presence of the peroxidase. The absence or presence of antibody binding may be determined by various methods, including flow cytometry of dissociated cells, microscopy, radiography, scintillation counting, *etc.*

MODULATION OF GENE EXPRESSION

The K+Hnov genes, gene fragments, or the encoded protein or protein fragments are useful in gene therapy to treat disorders associated with K+Hnov defects. Expression vectors may be used to introduce the K+Hnov gene into a cell. Such vectors generally have convenient restriction sites located near the promoter sequence to provide for the insertion of nucleic acid sequences. Transcription cassettes may be prepared comprising a transcription initiation region, the target gene or fragment thereof, and a transcriptional termination region. The transcription cassettes may be introduced into a variety of vectors, *e.g.* plasmid; retrovirus, *e.g.* lentivirus; adenovirus; and the like, where the vectors are able to transiently or stably be maintained in the cells, usually for a period of at least about one day, more usually for a period of at least about several days to several weeks.

The gene or K+Hnov protein may be introduced into tissues or host cells by any number of routes, including viral infection, microinjection, or fusion of vesicles. Jet injection may also be used for intramuscular administration, as

described by Furth *et al.* (1992) Anal Biochem **205**:365-368. The DNA may be coated onto gold microparticles, and delivered intradermally by a particle bombardment device, or "gene gun" as described in the literature (see, for example, Tang *et al.* (1992) Nature **356**:152-154), where gold microprojectiles are coated with the K+Hnov or DNA, then bombarded into skin cells.

Antisense molecules can be used to down-regulate expression of K+Hnov in cells. The anti-sense reagent may be antisense oligonucleotides (ODN), particularly synthetic ODN having chemical modifications from native nucleic acids, or nucleic acid constructs that express such anti-sense molecules as RNA. The antisense sequence is complementary to the mRNA of the targeted gene, and inhibits expression of the targeted gene products. Antisense molecules inhibit gene expression through various mechanisms, *e.g.* by reducing the amount of mRNA available for translation, through activation of RNAse H, or steric hindrance. One or a combination of antisense molecules may be administered, where a combination may comprise multiple different sequences.

Antisense molecules may be produced by expression of all or a part of the target gene sequence in an appropriate vector, where the transcriptional initiation is oriented such that an antisense strand is produced as an RNA molecule. Alternatively, the antisense molecule is a synthetic oligonucleotide. Antisense oligonucleotides will generally be at least about 7, usually at least about 12, more usually at least about 20 nucleotides in length, and not more than about 500, usually not more than about 50, more usually not more than about 35 nucleotides in length, where the length is governed by efficiency of inhibition, specificity, including absence of cross-reactivity, and the like. It has been found that short oligonucleotides, of from 7 to 8 bases in length, can be strong and selective inhibitors of gene expression (see Wagner *et al.* (1996) Nature Biotechnology **14**:840-844).

A specific region or regions of the endogenous sense strand mRNA sequence is chosen to be complemented by the antisense sequence. Selection of a specific sequence for the oligonucleotide may use an empirical method, where several candidate sequences are assayed for inhibition of expression of

the target gene in an *in vitro* or animal model. A combination of sequences may also be used, where several regions of the mRNA sequence are selected for antisense complementation.

Antisense oligonucleotides may be chemically synthesized by methods known in the art (see Wagner *et al.* (1993) *supra.* and Milligan *et al., supra.*) Preferred oligonucleotides are chemically modified from the native phosphodiester structure, in order to increase their intracellular stability and binding affinity. A number of such modifications have been described in the literature, which alter the chemistry of the backbone, sugars or heterocyclic bases.

Among useful changes in the backbone chemistry are phosphorothioates; phosphorodithioates, where both of the non-bridging oxygens are substituted with sulfur; phosphoroamidites; alkyl phosphotriesters and boranophosphates. Achiral phosphate derivatives include 3'-O'-5'-S-phosphorothioate, 3'-S-5'-O-phosphorothioate, 3'-CH2-5'-O-phosphonate and 3'-NH-5'-O-phosphoroamidate. Peptide nucleic acids replace the entire ribose phosphodiester backbone with a peptide linkage. Sugar modifications are also used to enhance stability and affinity. The α-anomer of deoxyribose may be used, where the base is inverted with respect to the natural β-anomer. The 2'-OH of the ribose sugar may be altered to form 2'-O-methyl or 2'-O-allyl sugars, which provides resistance to degradation without comprising affinity. Modification of the heterocyclic bases must maintain proper base pairing. Some useful substitutions include deoxyuridine for deoxythymidine; 5-methyl-2'-deoxycytidine and 5-bromo-2'-deoxycytidine for deoxycytidine. 5- propynyl-2'-deoxyuridine and 5-propynyl-2'-deoxycytidine have been shown to increase affinity and biological activity when substituted for deoxythymidine and deoxycytidine, respectively.

As an alternative to anti-sense inhibitors, catalytic nucleic acid compounds, *e.g.* ribozymes, anti-sense conjugates, *etc.* may be used to inhibit gene expression. Ribozymes may be synthesized *in vitro* and administered to the patient, or may be encoded on an expression vector, from which the ribozyme is synthesized in the targeted cell (for example, see International patent application

WO 9523225, and Beigelman et al. (1995) <u>Nucl. Acids Res</u> **23**:4434-42). Examples of oligonucleotides with catalytic activity are described in WO 9506764. Conjugates of anti-sense ODN with a metal complex, *e.g.* terpyridylCu(II), capable of mediating mRNA hydrolysis are described in Bashkin *et al.* (1995) <u>Appl Biochem Biotechnol</u> 54:43-56.

GENETICALLY ALTERED CELL OR ANIMAL MODELS FOR K+HNOV FUNCTION

The subject nucleic acids can be used to generate transgenic animals or site specific gene modifications in cell lines. Transgenic animals may be made through homologous recombination, where the normal *K+Hnov* locus is altered. Alternatively, a nucleic acid construct is randomly integrated into the genome. Vectors for stable integration include plasmids, retroviruses and other animal viruses, YACs, and the like.

The modified cells or animals are useful in the study of *K+Hnov* function and regulation. For example, a series of small deletions and/or substitutions may be made in the *K+Hnov* gene to determine the role of different transmembrane domains in forming multimeric structures, ion channels, *etc.* Of interest are the use of *K+Hnov* to construct transgenic animal models for epilepsy and other neurological defects, where expression of K+Hnov is specifically reduced or absent. Specific constructs of interest include anti-sense *K+Hnov*, which will block K+Hnov expression, expression of dominant negative K+Hnov mutations, *etc.* One may also provide for expression of the *K+Hnov* gene or variants thereof in cells or tissues where it is not normally expressed or at abnormal times of development.

DNA constructs for homologous recombination will comprise at least a portion of the *K+Hnov* gene with the desired genetic modification, and will include regions of homology to the target locus. DNA constructs for random integration need not include regions of homology to mediate recombination. Conveniently, markers for positive and negative selection are included. Methods for generating cells having targeted gene modifications through homologous recombination are

known in the art. For various techniques for transfecting mammalian cells, see Keown *et al.* (1990) Methods in Enzymology 185:527-537.

For embryonic stem (ES) cells, an ES cell line may be employed, or embryonic cells may be obtained freshly from a host, *e.g.* mouse, rat, guinea pig, *etc.* Such cells are grown on an appropriate fibroblast-feeder layer or grown in the presence of leukemia inhibiting factor (LIF). When ES or embryonic cells have been transformed, they may be used to produce transgenic animals. After transformation, the cells are plated onto a feeder layer in an appropriate medium. Cells containing the construct may be detected by employing a selective medium. After sufficient time for colonies to grow, they are picked and analyzed for the occurrence of homologous recombination or integration of the construct. Those colonies that are positive may then be used for embryo manipulation and blastocyst injection. Blastocysts are obtained from 4 to 6 week old superovulated females. The ES cells are trypsinized, and the modified cells are injected into the blastocoel of the blastocyst. After injection, the blastocysts are returned to each uterine horn of pseudopregnant females. Females are then allowed to go to term and the resulting offspring screened for the construct. By providing for a different phenotype of the blastocyst and the genetically modified cells, chimeric progeny can be readily detected.

The chimeric animals are screened for the presence of the modified gene and males and females having the modification are mated to produce homozygous progeny. If the gene alterations cause lethality at some point in development, tissues or organs can be maintained as allogeneic or congenic grafts or transplants, or in *in vitro* culture. The transgenic animals may be any non-human mammal, such as laboratory animals, domestic animals, etc. The transgenic animals may be used in functional studies, drug screening, *etc.*, *e.g.* to determine the effect of a candidate drug on Ras or related gene activation, oncogenesis, *etc.*

TESTING OF K+HNOV FUNCTION and RESPONSES

Potassium channels such as K+Hnov polypeptides are involved in multiple biologically important processes. Pharmacological agents designed to affect only specific channel subtypes are of particular interest. Presently available compounds tend to be non-specific and elicit both positive and negative responses, thereby reducing clinical efficacy.

The subject polypeptides may be used in *in vitro* and *in vivo* models to test the specificity of novel compounds, and of analogs and derivatives of compounds known to act on potassium channels. Numerous pharmacological agents have profound affects on K+ channel activity. As examples, Sotalol (BETAPACE) is a class III antiarrhythmic drug that prolongs cardiac action potentials by inhibiting delayed rectifier K+ channels. Sulfonylurea drugs, such as Glipizide (GLUCOTROL) and Tolazamide (TOLAMIDE) function as antidiabetic drugs by blocking ATP-sensitive K+ channels present in pancreatic islet cells, thereby regulating insulin secretion. Diazoxide (HYPERSTAT IV) is an antihypertensive drug that activates ATP-sensitive K+ channels, resulting in the relaxation of vascular smooth muscle. There are several other examples of drugs that have antidiabetic, antihypertensive, or antiarrhythmic activities. A number of drugs that activate K+ channels that have been proposed as coronary vasodilators for the treatment of both vasospastic and chronic stable angina.

The availability of multiple K+ channel subunits allows *in vitro* reconstruction of functional channels, which may comprise different alpha and beta subunits. The individual components may be modified by sequence deletion, substitution, *etc.* to determine the functional role of specific domains.

Drug screening may be performed using an *in vitro* model, a genetically altered cell or animal, or purified K+Hnov protein, either as monomers, homomultimers or hetermultimers. One can identify ligands or substrates that bind to, modulate or mimic the action of *K+Hnov*. Drug screening identifies agents that provide a replacement for K+Hnov function in abnormal cells. Of particular interest are screening assays for agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including

monitoring cellular excitation and conductance, labeled *in vitro* protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, and the like. The purified protein may also be used for determination of three-dimensional crystal structure, which can be used for modeling intermolecular interactions.

The term "agent" as used herein describes any molecule, *e.g.* protein or pharmaceutical, with the capability of altering or mimicking the physiological function of *K+Hnov* polypeptide. Generally a plurality of assay mixtures are run in parallel with different agent concentrations to obtain a differential response to the various concentrations. Typically, one of these concentrations serves as a negative control, *i.e.* at zero concentration or below the level of detection.

Candidate agents encompass numerous chemical classes, though typically they are organic molecules, preferably small organic compounds having a molecular weight of more than 50 and less than about 2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof.

Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides and oligopeptides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means, and may be used to produce combinatorial libraries. Known

pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification, *etc.* to produce structural analogs.

Where the screening assay is a binding assay, one or more of the molecules may be joined to a label, where the label can directly or indirectly provide a detectable signal. Various labels include radioisotopes, fluorescers, chemiluminescers, enzymes, specific binding molecules, particles, *e.g.* magnetic particles, and the like. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin etc. For the specific binding members, the complementary member would normally be labeled with a molecule that provides for detection, in accordance with known procedures.

A variety of other reagents may be included in the screening assay. These include reagents like salts, neutral proteins, e.g. albumin, detergents, etc that are used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Reagents that improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, *etc.* may be used. The mixture of components are added in any order that provides for the requisite binding. Incubations are performed at any suitable temperature, typically between 4 and 40°C. Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high-throughput screening. Typically between 0.1 and 1 hours will be sufficient.

The compounds having the desired pharmacological activity may be administered in a physiologically acceptable carrier to a host in a variety of ways, orally, topically, parenterally *e.g.* subcutaneously, intraperitoneally, by viral infection, intravascularly, *etc.* Depending upon the manner of introduction, the compounds may be formulated in a variety of ways. The concentration of therapeutically active compound in the formulation may vary from about 0.1-100 wt.%. The pharmaceutical compositions can be prepared in various forms, such as granules, tablets, pills, suppositories, capsules, suspensions, salves, lotions and the like. Pharmaceutical grade organic or inorganic carriers and/or diluents suitable for oral and topical use can be used to make up

compositions containing the therapeutically-active compounds. Diluents known to the art include aqueous media, vegetable and animal oils and fats. Stabilizing agents, wetting and emulsifying agents, salts for varying the osmotic pressure or buffers for securing an adequate pH value, and skin penetration enhancers can be used as auxiliary agents.

It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, and reagents described, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

As used herein the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the cell" includes reference to one or more cells and equivalents thereof known to those skilled in the art, and so forth. All technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise.

It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a complex" includes a plurality of such complexes and reference to "the formulation" includes reference to one or more formulations and equivalents thereof known to those skilled in the art, and so forth.

All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing, for example, the methods and methodologies that are described in the publications which might be used in connection with the presently described invention. The publications discussed above and throughout the text are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an

admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention.

EXPERIMENTAL

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the subject invention, and are not intended to limit the scope of what is regarded as the invention. Efforts have been made to ensure accuracy with respect to the numbers used (*e.g.* amounts, temperature, concentrations, *etc.*) but some experimental errors and deviations should be allowed for. Unless otherwise indicated, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees centigrade; and pressure is at or near atmospheric.

Methods

Two different types of sequence searches were performed. The first centered on the most highly conserved region of the K+ channel family, the pore domain. The pore is composed of 15-17 amino acids and can be divided into subfamilies based on the number of transmembrane segments present in the channel. Eleven variant peptide sequences corresponding to the pore domain were used in TBLASTN searches against the EST division of Genbank. Significant matches were identified, and classified into 2 categories: identical to known human K+ channels and related to known K+ channels. The pore sequences are shown in Table 2.

TABLE 2

SEQ ID NO	Genbank #	
49	L02751	TGGTGGGCTGTGGTGACCATGACAACTGTGGGCTATGGGGACATG
50	M60451	TGGTGGGCAGTGGTCACCATGACCACTGTGGGCTACGGGGACATG
51	L02752	TGGTGGGCAGTCGTCTCCATGACAACTGTAGGCTATGGAGACATG
52	M55515	TGGTGGGCAGTGGTAACCATGACAACAGTGGGTTACGGCGATATG
53	Z11585	TGGTGGGCTGTGGTCACCATGACGACCCTGGGCTATGGAGACATG
54	U40990	TGGTGGGGGGTGGTCACAGTCACCACCATCGGCTATGGGGACAAG
55	I26643	TGGTGGGCAGTGGTCACCATGACCACGGTTGGCTATGGGGACATG
56	M96747	TGGTGGGCCGTGGTCACCATGACGACCCTGGGCTATGGAGACATG
57	M84676	TGGTGGGCTGTGGTCACCATGACGACACTGGGCTACGGAGACATG
58	M55514	TGGTGGGCTGTGGTGACCATGACAACTGTGGGCTATGGGGACATG
59	X83582	TTCCTGTTCTCCATTGAGACCGAAACAACCATTGGGTATGGCTTCCG
60	S78684	TTTTTATTCTCAATAGAGACAGAAACCACCATTGGTTATGGCTACCG
61	U22413	TTCCTCTTCTCCATTGAGACCCAGACAACCATAGGCTATGGTTTCAG
62	U24056	TTCCTGTTCTCGGTGGAGACGCAGACGACCATCGGCTATGGGTTCCG
63	U52155	TTCCTCTTCTCCCTTGAATCCCAAACCACCATTGGCTATGGCTTCCG
64	D87291	TTTCTCTTTTCCCTGGAATCCCAGACAACCATTGGCTATGGAGTCCG
65	D50582	TTCCTTTTCTCCATTGAGGTCCAAGTGACTATTGGCTTTGGGGGGCG
66	D50315	TTTCTCTTCTCCATTGAAGTTCAAGTTACCATTGGGTTTGGAGGGAG
67	U04270	GCGCTCTACTTCACCTTCAGCAGCCTCACCAGTGTGGGCTTCGGCAAC

The unique pore peptides sequences are shown in Table 3.

TABLE 3

SEQ ID NO	Amino acid sequence
68	WWAVVSMTTVGYGDM
69	WWAVVTMTTLGYGDM
70	WWGVVTVTTIGYGDK
71	WWAVVTMTTVGYGDM
72	FLFSIEVQVTIGFGG
73	FLFSLESQTTIGYGV
74	FLFSIETETTIGYGY
75	FLFSIETQTTIGYGF
76	FLFSVETQTTIGYGF
77	FLFSLESQTTIGYGF
78	FLFSIETETTIGYGF
79	ALYFTFSSLTSVGFGN

The second set of experiments was based on a complex, reiterative process. Annotated protein and DNA sequences were obtained from GenBank for all known K+ channels from all species. The TBLASTN and BLASTN programs were used to identify homologous ESTs, which were then analyzed using the BLASTX and BLASTN algorithms to identify ESTs which were related to K+ channels yet not identical to any known human K+ channel gene.

Novel human K+ channels were defined as those that had clear homology to known K+ channels from any species and were not present as identities or near identities to any human-derived sequences in any division of Genbank.

Isolation of full length cDNA sequence. EST clones were picked from the IMAGE consortium cDNA library and end-sequenced with vector primers. Gap closure was achieved either by primer walking or transposon sequencing. GeneTrapper (Life

Technologies) was used to isolate larger cDNA clones according to the provided protocol. RACE was used to extend the sequences as necessary using standard protocols.

Sequences were assembled in Sequencher (Gene Codes). The presence of open reading frames was assessed as well as potential start codons. Potential polymorphisms were detected as sequence variants between multiple independent clones. Sequence homologies were detected using the BLAST algorithms.

The completed gene sequences and predicted amino acid sequences are provided as SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21-24, 26 and 28-29. Polymorphisms, chromosome locations and family assignments are shown in Table 1.

ESTs that had top human hits with >95% identity over 100 amino acids were discarded. This was based upon the inventors' experience that these sequences were usually identical to the starting probe sequences, with the differences due to sequence error. The remaining BLASTN and BLASTX outputs for each EST were examined manually, *i.e.*, ESTs were removed from the analysis if the inventors determined that the variation from the known related probe sequence was a result of poor database sequence. Poor database sequence was usually identified as a number of 'N' nucleotides in the database sequence for a BLASTN search and as a base deletion or insertion in the database sequence, resulting in a peptide frameshift, for a BLASTX output. ESTs for which the highest scoring match was to non-related sequences were also discarded at this stage. The EST sequences that correspond to each clone are shown in Table 4.

Table 4

Genbank Accession#	K+Hnov	clone ID	Trace	IMAGE Plate Coordinates	Read 5'/3'
N39619	K+Hnov2	277113	yy51h05.s1	611p10	3'
N46767	K+Hnov2	277113	yy51h05.r1	611p10	5'
R19352	K+Hnov11	33144	yg24f12.r1	155o24	5'
R44628	K+Hnov11	33144	yg24f12.s1	155o24	3'

R35526	K+Hnov14	37299	yg64e08.r1	165o15	5'
R73353	K+Hnov14	157854	yl10e04.r1	251g07	5'
AA397616	K+Hnov14	728558	zt79c08.r1	1787j15	5'
AA286692	K+Hnov28	700757	zs48h03.r1	1715d6	5'
AA150494	K+Hnov42	491748	zl08e07.s1	1170o13	3'
AA156697	K+Hnov42	491748	zl08e07.r1	1170o13	5'
AA191752	K+Hnov42	626699	zp82d06.r1	1522f12	5'
AA216446	K+Hnov42	626699	zp82d06.s1	1522f12	3'
AA430591	K+Hnov42	773611	zw51f10.r1	1904o20	5'
AA236930	K+Hnov44	683888	zs01a05.s1	1671e9	3'
AA236968	K+Hnov44	683888	zs01a05.r1	1671e9	5'

Example 2: Chromosomal Localization

Two primers were designed in the 3'-untranslated regions of each gene sequence to amplify a product across the Stanford G3 radiation hybrid map, or the Whitehead GB4 panel. The PCR data were submitted for automatic two-point analysis. Mapping data were correlated with cytoband information and comparisons with the OMIM human gene map data base were made. The following primers were made:

K+Hnov1 on GB4
(SEQ ID NO:31) F: 5' TATCCACATCAATGGACAAAGC 3'
(SEQ ID NO:32) R: 5' TGCATAACTGGCTGGGTGTA 3'
Results: 1.71 cR from D2S331, Cytogenetic location of 2q37

K+Hnov2 on G3
F: 5' GTCAGGTGACCGAGTTCA 3'
R: 5' GCTCCATCTCCAGATTCTTC 3'
Results: 0.0 cR from SHGC-1320, Cytogenetic location of 11q12

K+Hnov6 on GB4
(SEQ ID NO:33) F: 5' TGACATCACTGGATGAACTTGA 3'
(SEQ ID NO:34) R: 5' TGCCTGCAAAGTTTGAACAT 3'
Results: 5.23 cR from WI-5509, Cytogenetic location of 2p23

K+Hnov9 on GB4
(SEQ ID NO:35) F: 5' TGACATCACTGGATGAACTTGA 3'
(SEQ ID NO:36) R: 5' TGCCTGCAAAGTTTGAACAT 3'

Results: 1.21 cR from AFM200VC7, Cytogenetic location of 8q23

K+Hnov11 on GB4
(SEQ ID NO:37) F: 5' ACCTGGTGGTATGGAAGCAT 3'
(SEQ ID NO:38) R: 5' TTTCTCCTGGCCTCTACCC 3'
Results: 2.43 cR from WI-6756, Cytogenetic location of 8q23

K+Hnov12 on G3
(SEQ ID NO:39) F: 5' TCCCTCTTGGGTGACCTTC 3'
(SEQ ID NO:40) R: 5' ATCTTTGTCAGCCACCAGCT 3'
Results: 7.45 cR from SHGC-32925, Cytogenetic location of Xp21

K+Hnov14 on GB4
(SEQ ID NO:41) F: 5' AGGTGTGCTGCCATCTGCTGTTCG3'
(SEQ ID NO:42) R: 5' AGCCTATCCTCTCTGAGAGTCAGG
Results: 7.69 cR from WI-7107, Cytogenetic location of 12q14

K+Hnov28 on GB4
(SEQ ID NO:43) F: 5' AAGCAGAGTACTCATGATGCC 3'
(SEQ ID NO:44) R: 5' TCTGGTAGACAGTACAGTGG 3'
Results: 35.38 cR from WI-9695, Cytogenetic location of 3q29

K+Hnov42 on G3
(SEQ ID NO:45) F: 5' CATTTGGCTGGTCCAAGATG 3'
(SEQ ID NO:46) R: 5' AGTCATTGGTAGGGAGGTAC 3'
Results: 7.45 cR from SHGC-32925, Cytogenetic location of Xp21

K+Hnov44 on G3
(SEQ ID NO:47) F: 5' CATGCTTCTACAGTCCAGCC 3'
(SEQ ID NO:48) R: 5' GGTCCTCAGTTGCAGAAATC 3'
Results: 7.45 cR from SHGC-32925, Cytogenetic location of Xp21

Map positions for K+Hnov15 and K+Hnov27 were obtained from public databases. K+Hnov2 and K+Hnov4 have not been mapped.

Example 3: Expression Analysis

RT-PCR was utilized to characterize the expression pattern of the novel ion channels. This approach used RNA from 30 different tissues to generate first strand cDNA. Total RNA was purchased (Clontech, Invitrogen) and used to synthesize first strand cDNA using M-MLV reverse transcriptase and the supplied buffer (Gibco-BRL). The 20 µl reaction contained 5 µg total RNA, 100 ng of random primers, 10 mM DTT,

0.5 mM each dNTP, and an RNAse inhibitor (Gibco-BRL). Identical reactions were set up without reverse transcriptase to control for DNA contamination in the RNA samples. The synthesis reaction proceeded for 1 hour at 37°C followed by 10 minutes at 95°C. These cDNAs, along with control cDNA synthesis reactions without reverse transcriptase, were diluted 1:5 and 2 µl of each sample were arrayed into 96-well trays, dried, and resuspended in PCR buffer prior to PCR amplification. The cDNAs were tested with primers with defined expression patterns to verify the presence of amplifiable cDNA from each tissue. Gene-specific primers were used to amplify the cDNAs in 20 µl PCR reactions with standard conditions, 2.5 mM $MgCl_2$, Taq Gold, and an appropriate annealing temperature.

This approach provides for relatively high-throughput analysis of gene expression in a large set of tissues in a cost-efficient manner and provides qualitative analysis of gene expression only. Modifications can be employed, such as the use of internal control primers, limited cycling parameters, and dilution series to convert this to a quantitative experiment.

Table 3

Anchor name	Adipose	Adrenal Gland	Bladder	Brain	Cerebellum	Cervix	Colon	Esophagus	Fetal Brain	Fetal Liver	Heart	HeLa Cells	Kidney	Liver	Lung	Mammary Gland	Pancreas	Placenta	Prostate	Rectum	Salivary Gland	Skeletal Muscle	Skin	Small Intestine	Spleen	Stomach	Testis	Thymus	Trachea	Uterus
K+Hnov1	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+
K+Hnov2	+		+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	-	+		+	+	+	-	+
K+Hnov4		-	-	+	+		+		+	-	-	-	-	-	-	+	-	-	+		+	+		+	-	-	-	-	-	-
K+Hnov6		+	+	+	+		+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
K+Hnov9		+	-	+	+		-		-	-	-	-	+	-	-	-	+	-		-	+		-	-	+	-	+	+	+	
K+Hnov11			+	+	+		-		+	+	+	+	+	+	+	+	+	+	+		+			+		+		-	+	+
K+Hnov12	+	+	+	-	-	-	-	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	+
K+Hnov14	-	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+
K+Hnov15		+	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+
K+Hnov27	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
K+Hnov28	-	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+
K+Hnov42																														
K+Hnov44	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+

A "+" indicates expression in the tissue, a "-" indicates no expression, and blank square indicates no data for that sample.

K+Hnov49 on Whitehead GB4 RH mapping panel:

Primer 1 (SEQ ID NO:5): 5' - CATAGCCATAGGTGAGGACT - 3'

Primer 2: (SEQ ID N:6) 5' - GAGAGGAAAACAGTCTGGGC - 3'

Results: Cytogenetic location 1q41, 4.6cR from framework marker D1S217

K+Hnov59 on Whitehead GB4 RH mapping panel

Primer 1 (SEQ ID NO:7): 5' - GGACATCGAACTAAGACCTG - 3'

Primer 2 (SEQ ID NO:8): 5' - TCCCATGCCATTCAGATCTG - 3'

Results: Cytogenetic location 19q13.2, 8.34cr from framework marker D19S425

EXPRESSION ANALYSIS OF K+HNOV49

A probe was created from a fragment corresponding to nucleotides 50 to 1284 of SEQ ID NO:83 (K+Hnov49) and purified DNA fragment was labeled with [^{32}P]dCTP (Amersham) by the random primer method. Adult human Multiple Tissue Northern (MTM™) Blots (Clontech) were hybridized with the [^{32}P]-labeled fragment in ExpressHyb™ solution (Clontech) for four hours, washed to a final stringency of 0.1xSSC, 0.1% SDS at 65°C and subjected to autoradiography for 24 hours.

Analysis revealed that K+Hnov49 is expressed as an approximately 4.2kb mRNA. Expression levels of K+Hnov49 are high in brain and liver and low in kidney tissues. No mRNA was detectable on these Northern blots for heart, skeletal muscle, colon, thymus, spleen, small intestine, placenta, lung or peripheral blood leukocytes indicating either a very low level of expression or that it is not expressed in these tissues. Expression analysis was also carried out by RT-PCR across an extended series of tissues. The results of these analyses are shown in Table 4. Primer pairs used for amplification of K+Hnov49 and 59 are the same as those used for RH mapping as indicated above.

Table 4

	Adipose	Adrenal Gland	Bladder	Brain	Cerebellum	Cervix	Colon	Esophagus	Fetal Brain	Fetal Liver	Heart	HeLa Cell	Kidney	Liver	Lung	Mammary Gland	Pancreas	Placenta	Prostate	Rectum	Salivary Gland	Skeletal Muscle	Skin	Small Intestine	Spleen	Stomach	Testis	Thymus	Trachea	Uterus
#49	+	+	+	+	+	+	-	+	+	-	+	+	+	-	+	+	-	-	+	-	+	+	-	+	-	+	+	+	-	-
#59	-	-	-	-	-	+	-	+	-	+	+	-	-	+	+	+	+	-	+	+	+	-	-	+	+	+	+	+	+	+

WHAT IS CLAIMED IS:

1. An isolated nucleic acid encoding a mammalian K+Hnov protein.

2. An isolated nucleic acid according to Claim 1, wherein said K+Hnov protein has the amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 27, 30, 81 or 83.

3. An isolated nucleic acid according to Claim 1, wherein said K+Hnov protein has an amino acid sequence that is substantially identical to the amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 27, 30, 81 or 83.

4. An isolated nucleic acid according to Claim 1 wherein the nucleotide sequence of said nucleic acid is SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, 23, 24, 26, 28, 29, 80 or 82.

5. An isolated nucleic acid that hybridizes under stringent conditions to a nucleic acid sequence of claim 4.

6. An expression cassette comprising a transcriptional initiation region functional in an expression host, a nucleic acid having a sequence of the isolated nucleic acid according to Claim 1 under the transcriptional regulation of said transcriptional initiation region, and a transcriptional termination region functional in said expression host.

7. A cell comprising an expression cassette according to Claim 6 as part of an extrachromosomal element or integrated into the genome of a host cell as a result of introduction of said expression cassette into said host cell, and the cellular progeny of said host cell.

8. A method for producing mammalian K+Hnov protein, said method comprising:

growing a cell according to Claim 7, whereby said mammalian K+Hnov protein is expressed; and

isolating said K+Hnov protein free of other proteins.

9. A purified polypeptide composition comprising at least 50 weight % of the protein present as a K+Hnov protein or a fragment thereof.

10. A monoclonal antibody binding specifically to a K+Hnov protein.

11. A non-human transgenic animal model for K+Hnov gene function wherein said transgenic animal comprises an introduced alteration in a K+Hnov gene.

12. The animal model of claim 11, wherein said animal is heterozygous for said introduced alteration.

13. The animal model of claim 12, wherein said animal is homozygous for said introduced alteration.

14. The animal model of claim 12, wherein said introduced alteration is a knockout of endogenous K+Hnov gene expression.

SEQUENCE LISTING

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gag gcg tcg gag aag atc atc atc aac gtg ggc ggc acg cga cat gag      164
Glu Ala Ser Glu Lys Ile Ile Ile Asn Val Gly Gly Thr Arg His Glu
 5                  10                  15                  20

acc tac cgc agc acc ctg cgc acc cta ccg gga acc cgc ctc gcc tgg      212
Thr Tyr Arg Ser Thr Leu Arg Thr Leu Pro Gly Thr Arg Leu Ala Trp
                25                  30                  35

ctg gcc gac ccc gac ggc ggg ggc cgg ccc gag acc gat ggc ggc ggt      260
Leu Ala Asp Pro Asp Gly Gly Gly Arg Pro Glu Thr Asp Gly Gly Gly
            40                  45                  50
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gtg ggt agc agc ggc agc agc ggc ggc ggg ggc tgc gag ttc ttc ttc     308
Val Gly Ser Ser Gly Ser Ser Gly Gly Gly Gly Cys Glu Phe Phe Phe
         55                  60                  65

gac agg cac ccg ggc gtc ttc gcc tac gtg ctc aac tac tac cgc acc     356
Asp Arg His Pro Gly Val Phe Ala Tyr Val Leu Asn Tyr Tyr Arg Thr
     70                  75                  80

ggc aag ctg cac tgc ccc gca gac gtg tgc ggg ccg ctc ttc gag gag     404
Gly Lys Leu His Cys Pro Ala Asp Val Cys Gly Pro Leu Phe Glu Glu
 85                  90                  95                 100

gag ctg gcc ttc tgg ggc atc gac gag acc gac gtg gag ccc tgc tgc     452
Glu Leu Ala Phe Trp Gly Ile Asp Glu Thr Asp Val Glu Pro Cys Cys
                105                 110                 115

tgg atg acc tac cgg cag cac cgc gac gcc gag gag gcg ctg gac atc     500
Trp Met Thr Tyr Arg Gln His Arg Asp Ala Glu Glu Ala Leu Asp Ile
            120                 125                 130

ttc gag acc ccc gac ctc att ggc ggc gac ccc ggc gac gac gag gac     548
Phe Glu Thr Pro Asp Leu Ile Gly Gly Asp Pro Gly Asp Asp Glu Asp
        135                 140                 145

ctg gcg gcc aag agg ctg ggc atc gag gac gcg gcg ggg ctc ggg ggc     596
Leu Ala Ala Lys Arg Leu Gly Ile Glu Asp Ala Ala Gly Leu Gly Gly
    150                 155                 160

ccc gac ggc aaa tct ggc cgc tgg agg agg ctg cag ccc cgc atg tgg     644
Pro Asp Gly Lys Ser Gly Arg Trp Arg Arg Leu Gln Pro Arg Met Trp
165                 170                 175                 180

gcc ctc ttc gaa gac ccc tac tcg tcc aga gcc gcc agg ttt att gct     692
Ala Leu Phe Glu Asp Pro Tyr Ser Ser Arg Ala Ala Arg Phe Ile Ala
                185                 190                 195

ttt gct tct tta ttc ttc atc ctg gtt tca att aca act ttt tgc ctg     740
Phe Ala Ser Leu Phe Phe Ile Leu Val Ser Ile Thr Thr Phe Cys Leu
            200                 205                 210

gaa aca cat gaa gct ttc aat att gtt aaa aac aag aca gaa cca gtc     788
Glu Thr His Glu Ala Phe Asn Ile Val Lys Asn Lys Thr Glu Pro Val
        215                 220                 225

atc aat ggc aca agt gtt gtt cta cag tat gaa att gaa acg gat cct     836
Ile Asn Gly Thr Ser Val Val Leu Gln Tyr Glu Ile Glu Thr Asp Pro
    230                 235                 240

gcc ttg acg tat gta gaa gga gtg tgt gtg gtg tgg ttt act ttt gaa     884
Ala Leu Thr Tyr Val Glu Gly Val Cys Val Val Trp Phe Thr Phe Glu
245                 250                 255                 260

ttt tta gtc cgt att gtt ttt tca ccc aat aaa ctt gaa ttc atc aaa     932
Phe Leu Val Arg Ile Val Phe Ser Pro Asn Lys Leu Glu Phe Ile Lys
                265                 270                 275

aat ctc ttg aat atc att gac ttt gtg gcc atc cta cct ttc tac tta     980
Asn Leu Leu Asn Ile Ile Asp Phe Val Ala Ile Leu Pro Phe Tyr Leu
            280                 285                 290

gag gtg gga ctc agt ggg ctg tca tcc aaa gct gct aaa gat gtg ctt    1028
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Glu Val Gly Leu Ser Gly Leu Ser Ser Lys Ala Ala Lys Asp Val Leu
295 300 305

ggc ttc ctc agg gtg gta agg ttt gtg agg atc ctg aga att ttc aag 1076
Gly Phe Leu Arg Val Val Arg Phe Val Arg Ile Leu Arg Ile Phe Lys
310 315 320

ctc acc cgc cat ttt gta ggt ctg agg gtg ctt gga cat act ctt cga 1124
Leu Thr Arg His Phe Val Gly Leu Arg Val Leu Gly His Thr Leu Arg
325 330 335 340

gct agt act aat gaa ttt ttg ctg ctg ata att ttc ctg gct cta gga 1172
Ala Ser Thr Asn Glu Phe Leu Leu Leu Ile Ile Phe Leu Ala Leu Gly
345 350 355

gtt ttg ata ttt gct acc atg atc tac tat gcc gag aga gtg gga gct 1220
Val Leu Ile Phe Ala Thr Met Ile Tyr Tyr Ala Glu Arg Val Gly Ala
360 365 370

caa cct aac gac cct tca gct agt gag cac aca cag ttc aaa aac att 1268
Gln Pro Asn Asp Pro Ser Ala Ser Glu His Thr Gln Phe Lys Asn Ile
375 380 385

ccc att ggg ttc tgg tgg gct gta gtg acc atg act acc ctg ggt tat 1316
Pro Ile Gly Phe Trp Trp Ala Val Val Thr Met Thr Thr Leu Gly Tyr
390 395 400

ggg gat atg tac ccc caa aca tgg tca ggc atg ctg gtg gga gcc ctg 1364
Gly Asp Met Tyr Pro Gln Thr Trp Ser Gly Met Leu Val Gly Ala Leu
405 410 415 420

tgt gct ctg gct gga gtg ctg aca ata gcc atg cca gtg cct gtc att 1412
Cys Ala Leu Ala Gly Val Leu Thr Ile Ala Met Pro Val Pro Val Ile
425 430 435

gtc aat aat ttt gga atg tac tac tcc ttg gca atg gca aag cag aaa 1460
Val Asn Asn Phe Gly Met Tyr Tyr Ser Leu Ala Met Ala Lys Gln Lys
440 445 450

ctt cca agg aaa aga aag aag cac atc cct cct gct cct cag gca agc 1508
Leu Pro Arg Lys Arg Lys Lys His Ile Pro Pro Ala Pro Gln Ala Ser
455 460 465

tca cct act ttt tgc aag aca gaa tta aat atg gcc tgc aat agt aca 1556
Ser Pro Thr Phe Cys Lys Thr Glu Leu Asn Met Ala Cys Asn Ser Thr
470 475 480

cag agt gac aca tgt ctg ggc aaa gac aat cga ctt ctg gaa cat aac 1604
Gln Ser Asp Thr Cys Leu Gly Lys Asp Asn Arg Leu Leu Glu His Asn
485 490 495 500

aga tca gtg tta tca ggt gac gac agt aca gga agt gag ccg cca cta 1652
Arg Ser Val Leu Ser Gly Asp Asp Ser Thr Gly Ser Glu Pro Pro Leu
505 510 515

tca ccc cca gaa agg ctc ccc atc aga cgc tct agt acc aga gac aaa 1700
Ser Pro Pro Glu Arg Leu Pro Ile Arg Arg Ser Ser Thr Arg Asp Lys
520 525 530

aac aga aga ggg gaa aca tgt ttc cta ctg acg aca ggt gat tac acg 1748
Asn Arg Arg Gly Glu Thr Cys Phe Leu Leu Thr Thr Gly Asp Tyr Thr

535 540 545

tgt gct tct gat gga ggg atc agg aaa gga tat gaa aaa tcc cga agc 1796
Cys Ala Ser Asp Gly Gly Ile Arg Lys Gly Tyr Glu Lys Ser Arg Ser
550 555 560

tta aac aac ata gcg ggc ttg gca ggc aat gct ctg agg ctc tct cca 1844
Leu Asn Asn Ile Ala Gly Leu Ala Gly Asn Ala Leu Arg Leu Ser Pro
565 570 575 580

gta aca tca ccc tac aac tct cct tgt cct ctg agg cgc tct cga tct 1892
Val Thr Ser Pro Tyr Asn Ser Pro Cys Pro Leu Arg Arg Ser Arg Ser
585 590 595

ccc atc cca tct atc t tgtaaaccaa accctcgtg 1927
Pro Ile Pro Ser Ile
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Arg Leu Ala Trp Leu Ala Asp Pro Asp Gly Gly Gly Arg Pro Glu Thr
35 40 45
Asp Gly Gly Gly Val Gly Ser Ser Gly Ser Ser Gly Gly Gly Gly Cys
50 55 60
Glu Phe Phe Phe Asp Arg His Pro Gly Val Phe Ala Tyr Val Leu Asn
65 70 75 80
Tyr Tyr Arg Thr Gly Lys Leu His Cys Pro Ala Asp Val Cys Gly Pro
85 90 95
Leu Phe Glu Glu Glu Leu Ala Phe Trp Gly Ile Asp Glu Thr Asp Val
100 105 110
Glu Pro Cys Cys Trp Met Thr Tyr Arg Gln His Arg Asp Ala Glu Glu
115 120 125
Ala Leu Asp Ile Phe Glu Thr Pro Asp Leu Ile Gly Gly Asp Pro Gly
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Asp Asp Glu Asp Leu Ala Ala Lys Arg Leu Gly Ile Glu Asp Ala Ala
145 150 155 160
Gly Leu Gly Gly Pro Asp Gly Lys Ser Gly Arg Trp Arg Arg Leu Gln
165 170 175
Pro Arg Met Trp Ala Leu Phe Glu Asp Pro Tyr Ser Ser Arg Ala Ala
180 185 190
Arg Phe Ile Ala Phe Ala Ser Leu Phe Phe Ile Leu Val Ser Ile Thr
195 200 205
Thr Phe Cys Leu Glu Thr His Glu Ala Phe Asn Ile Val Lys Asn Lys
210 215 220
Thr Glu Pro Val Ile Asn Gly Thr Ser Val Val Leu Gln Tyr Glu Ile
225 230 235 240
Glu Thr Asp Pro Ala Leu Thr Tyr Val Glu Gly Val Cys Val Val Trp
245 250 255
Phe Thr Phe Glu Phe Leu Val Arg Ile Val Phe Ser Pro Asn Lys Leu
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Glu Phe Ile Lys Asn Leu Leu Asn Ile Ile Asp Phe Val Ala Ile Leu
275 280 285

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Pro Phe Tyr Leu Glu Val Gly Leu Ser Gly Leu Ser Ser Lys Ala Ala
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Lys Asp Val Leu Gly Phe Leu Arg Val Val Arg Phe Val Arg Ile Leu
305                 310                 315                 320
Arg Ile Phe Lys Leu Thr Arg His Phe Val Gly Leu Arg Val Leu Gly
                325                 330                 335
His Thr Leu Arg Ala Ser Thr Asn Glu Phe Leu Leu Leu Ile Ile Phe
            340                 345                 350
Leu Ala Leu Gly Val Leu Ile Phe Ala Thr Met Ile Tyr Tyr Ala Glu
        355                 360                 365
Arg Val Gly Ala Gln Pro Asn Asp Pro Ser Ala Ser Glu His Thr Gln
    370                 375                 380
Phe Lys Asn Ile Pro Ile Gly Phe Trp Trp Ala Val Val Thr Met Thr
385                 390                 395                 400
Thr Leu Gly Tyr Gly Asp Met Tyr Pro Gln Thr Trp Ser Gly Met Leu
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Val Gly Ala Leu Cys Ala Leu Ala Gly Val Leu Thr Ile Ala Met Pro
            420                 425                 430
Val Pro Val Ile Val Asn Asn Phe Gly Met Tyr Tyr Ser Leu Ala Met
        435                 440                 445
Ala Lys Gln Lys Leu Pro Arg Lys Arg Lys Lys His Ile Pro Pro Ala
    450                 455                 460
Pro Gln Ala Ser Ser Pro Thr Phe Cys Lys Thr Glu Leu Asn Met Ala
465                 470                 475                 480
Cys Asn Ser Thr Gln Ser Asp Thr Cys Leu Gly Lys Asp Asn Arg Leu
                485                 490                 495
Leu Glu His Asn Arg Ser Val Leu Ser Gly Asp Asp Ser Thr Gly Ser
            500                 505                 510
Glu Pro Pro Leu Ser Pro Pro Glu Arg Leu Pro Ile Arg Arg Ser Ser
        515                 520                 525
Thr Arg Asp Lys Asn Arg Arg Gly Glu Thr Cys Phe Leu Leu Thr Thr
    530                 535                 540
Gly Asp Tyr Thr Cys Ala Ser Asp Gly Gly Ile Arg Lys Gly Tyr Glu
545                 550                 555                 560
Lys Ser Arg Ser Leu Asn Asn Ile Ala Gly Leu Ala Gly Asn Ala Leu
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Arg Ser Arg Ser Pro Ile Pro Ser Ile
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gagaacagga ttcttccctt ctttttggcc accaaatgcc tatgtgcacc acacattcca     180
gtgtgctgag aagggcagag cttcttggat gatgatggac gtccccaccgg gcaggatgaa    240
ggcagagcgt gtggcatctc cacctcaagg gtgcagcctg atcttcctct tctcccttgc     300
cagccagcac tctgccttct gtatccacc atg gtg ttt ggt gag ttt ttc cat       353
                                Met Val Phe Gly Glu Phe Phe His
                                1               5
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cgc cct gga caa gac gag gaa ctt gtc aac ctg aat gtg ggg ggc ttt 401
Arg Pro Gly Gln Asp Glu Glu Leu Val Asn Leu Asn Val Gly Gly Phe
10 15 20

aag cag tct gtt gac caa agc acc ctc ctg cgg ttt cct cac acc aga 449
Lys Gln Ser Val Asp Gln Ser Thr Leu Leu Arg Phe Pro His Thr Arg
25 30 35 40

ctg ggg aag ctg ctt act tgc cat tct gaa gag gcc att ctg gag ctg 497
Leu Gly Lys Leu Leu Thr Cys His Ser Glu Glu Ala Ile Leu Glu Leu
45 50 55

tgt gat gat tac agt gtg gcc gat aag gaa tac tac ttt gat cgg aat 545
Cys Asp Asp Tyr Ser Val Ala Asp Lys Glu Tyr Tyr Phe Asp Arg Asn
60 65 70

ccc tcc ttg ttc aga tat gtt ttg aat ttt tat tac acg ggg aag ctg 593
Pro Ser Leu Phe Arg Tyr Val Leu Asn Phe Tyr Tyr Thr Gly Lys Leu
75 80 85

cat gtc atg gag gag ctg tgc gta ttc tca ttc tgc cag gag atc gag 641
His Val Met Glu Glu Leu Cys Val Phe Ser Phe Cys Gln Glu Ile Glu
90 95 100

tac tgg ggc atc aac gag ctc ttc att gat tct tgc tgc agc aat cgc 689
Tyr Trp Gly Ile Asn Glu Leu Phe Ile Asp Ser Cys Cys Ser Asn Arg
105 110 115 120

tac cag gaa cgc aag gag gaa aac cac gag aag gac tgg gac cag aaa 737
Tyr Gln Glu Arg Lys Glu Glu Asn His Glu Lys Asp Trp Asp Gln Lys
125 130 135

agc cat gat gtg agt acc gac tcc tcg ttt gaa gag tcg tct ctg ttt 785
Ser His Asp Val Ser Thr Asp Ser Ser Phe Glu Glu Ser Ser Leu Phe
140 145 150

gag aaa gag ctg gag aag ttt gac aca ctg cga ttt ggt cag ctc cgg 833
Glu Lys Glu Leu Glu Lys Phe Asp Thr Leu Arg Phe Gly Gln Leu Arg
155 160 165

aag aaa atc tgg att aga atg gag aat cca gcg tac tgc ctg tcc gct 881
Lys Lys Ile Trp Ile Arg Met Glu Asn Pro Ala Tyr Cys Leu Ser Ala
170 175 180

aag ctt atc gct atc tcc tcc ttg agc gtg gtg ctg gcc tcc atc gtg 929
Lys Leu Ile Ala Ile Ser Ser Leu Ser Val Val Leu Ala Ser Ile Val
185 190 195 200

gcc atg tgc gtt cac agc atg tcg gag ttc cag aat gag gat gga gaa 977
Ala Met Cys Val His Ser Met Ser Glu Phe Gln Asn Glu Asp Gly Glu
205 210 215

gtg gat gat ccg gtg ctg gaa gga gtg gag atc gcg tgc att gcc tgg 1025
Val Asp Asp Pro Val Leu Glu Gly Val Glu Ile Ala Cys Ile Ala Trp
220 225 230

ttc acc ggg gag ctt gcc gtc cgg ctg gct gcc gct cct tgt caa aag 1073
Phe Thr Gly Glu Leu Ala Val Arg Leu Ala Ala Ala Pro Cys Gln Lys
235 240 245

aaa ttc tgg aaa aac cct ctg aac atc att gac ttt gtc tct att att 1121

Lys Phe Trp Lys Asn Pro Leu Asn Ile Ile Asp Phe Val Ser Ile Ile
250 255 260

ccc ttc tat gcc acg ttg gct gta gac acc aag gag gaa gag agt gag 1169
Pro Phe Tyr Ala Thr Leu Ala Val Asp Thr Lys Glu Glu Glu Ser Glu
265 270 275 280

gat att gag aac atg ggc aag gtg gtc cag atc cta cgg ctt atg agg 1217
Asp Ile Glu Asn Met Gly Lys Val Val Gln Ile Leu Arg Leu Met Arg
285 290 295

att ttc cga att cta aag ctt gcc cgg cac tcg gta gga ctt cgg tct 1265
Ile Phe Arg Ile Leu Lys Leu Ala Arg His Ser Val Gly Leu Arg Ser
300 305 310

cta ggt gcc aca ctg aga cac agc tac cat gaa gtt ggg ctt ctg ctt 1313
Leu Gly Ala Thr Leu Arg His Ser Tyr His Glu Val Gly Leu Leu Leu
315 320 325

ctc ttc ctc tct gtg ggc att tcc att ttc tct gtg ctt atc tac tcc 1361
Leu Phe Leu Ser Val Gly Ile Ser Ile Phe Ser Val Leu Ile Tyr Ser
330 335 340

gtg gag aaa gat gac cac aca tcc agc ctc acc agc atc ccc atc tgc 1409
Val Glu Lys Asp Asp His Thr Ser Ser Leu Thr Ser Ile Pro Ile Cys
345 350 355 360

tgg tgg tgg gcc acc atc agc atg aca act gtg ggc tat gga gac acc 1457
Trp Trp Trp Ala Thr Ile Ser Met Thr Thr Val Gly Tyr Gly Asp Thr
365 370 375

cac ccg gtc acc ttg gcg gga aag ctc atc gcc agc aca tgc atc atc 1505
His Pro Val Thr Leu Ala Gly Lys Leu Ile Ala Ser Thr Cys Ile Ile
380 385 390

tgt ggc atc ttg gtg gtg gcc ctt ccc atc acc atc atc ttc aac aag 1553
Cys Gly Ile Leu Val Val Ala Leu Pro Ile Thr Ile Ile Phe Asn Lys
395 400 405

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Phe Ser Lys Tyr Tyr Gln Lys Gln Lys Asp Ile Asp Val Asp Gln Cys
410 415 420

agt gag gat gca cca gag aag tgt cat gag cta cct tac ttt aac att 1649
Ser Glu Asp Ala Pro Glu Lys Cys His Glu Leu Pro Tyr Phe Asn Ile
425 430 435 440

agg gat ata tat gca cag cgg atg cac gcc ttc att acc agt ctc tct 1697
Arg Asp Ile Tyr Ala Gln Arg Met His Ala Phe Ile Thr Ser Leu Ser
445 450 455

tct gta ggc att gtg gtg agc gat cct gac tcc aca gat gct tca agc 1745
Ser Val Gly Ile Val Val Ser Asp Pro Asp Ser Thr Asp Ala Ser Ser
460 465 470

att gaa gac aat gag gac att tgt aac acc acc tcc ttg gag aat tgc 1793
Ile Glu Asp Asn Glu Asp Ile Cys Asn Thr Thr Ser Leu Glu Asn Cys
475 480 485

aca gca a aatgagcggg ggtgtttgtg cctgtttctc ttatcctttc ccaacattag 1850
Thr Ala

490

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cctttcagcc atagttggac attcattgct gaattctgaa atgatagaat tgtctttatt 1970
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gtgatagagt ttggaatata agataaatgg tattgggtgg ggtttgtggc tacagcttat 2090
gcatcattct gtgtttgtca tttactcaca ttgagctaac tttaaattac tgacaagtag 2150
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35 40 45
Ser Glu Glu Ala Ile Leu Glu Leu Cys Asp Asp Tyr Ser Val Ala Asp
50 55 60
Lys Glu Tyr Tyr Phe Asp Arg Asn Pro Ser Leu Phe Arg Tyr Val Leu
65 70 75 80
Asn Phe Tyr Tyr Thr Gly Lys Leu His Val Met Glu Glu Leu Cys Val
85 90 95
Phe Ser Phe Cys Gln Glu Ile Glu Tyr Trp Gly Ile Asn Glu Leu Phe
100 105 110
Ile Asp Ser Cys Cys Ser Asn Arg Tyr Gln Glu Arg Lys Glu Glu Asn
115 120 125
His Glu Lys Asp Trp Asp Gln Lys Ser His Asp Val Ser Thr Asp Ser
130 135 140
Ser Phe Glu Glu Ser Ser Leu Phe Glu Lys Glu Leu Glu Lys Phe Asp
145 150 155 160
Thr Leu Arg Phe Gly Gln Leu Arg Lys Lys Ile Trp Ile Arg Met Glu
165 170 175
Asn Pro Ala Tyr Cys Leu Ser Ala Lys Leu Ile Ala Ile Ser Ser Leu
180 185 190
Ser Val Val Leu Ala Ser Ile Val Ala Met Cys Val His Ser Met Ser
195 200 205
Glu Phe Gln Asn Glu Asp Gly Glu Val Asp Asp Pro Val Leu Glu Gly
210 215 220
Val Glu Ile Ala Cys Ile Ala Trp Phe Thr Gly Glu Leu Ala Val Arg
225 230 235 240
Leu Ala Ala Ala Pro Cys Gln Lys Lys Phe Trp Lys Asn Pro Leu Asn
245 250 255
Ile Ile Asp Phe Val Ser Ile Ile Pro Phe Tyr Ala Thr Leu Ala Val
260 265 270
Asp Thr Lys Glu Glu Glu Ser Glu Asp Ile Glu Asn Met Gly Lys Val
275 280 285
Val Gln Ile Leu Arg Leu Met Arg Ile Phe Arg Ile Leu Lys Leu Ala
290 295 300
Arg His Ser Val Gly Leu Arg Ser Leu Gly Ala Thr Leu Arg His Ser
305 310 315 320
Tyr His Glu Val Gly Leu Leu Leu Leu Phe Leu Ser Val Gly Ile Ser
325 330 335
Ile Phe Ser Val Leu Ile Tyr Ser Val Glu Lys Asp Asp His Thr Ser
340 345 350

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Ser Leu Thr Ser Ile Pro Ile Cys Trp Trp Trp Ala Thr Ile Ser Met
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Thr Thr Val Gly Tyr Gly Asp Thr His Pro Val Thr Leu Ala Gly Lys
    370                 375                 380
Leu Ile Ala Ser Thr Cys Ile Ile Cys Gly Ile Leu Val Val Ala Leu
385                 390                 395                 400
Pro Ile Thr Ile Ile Phe Asn Lys Phe Ser Lys Tyr Tyr Gln Lys Gln
                405                 410                 415
Lys Asp Ile Asp Val Asp Gln Cys Ser Glu Asp Ala Pro Glu Lys Cys
            420                 425                 430
His Glu Leu Pro Tyr Phe Asn Ile Arg Asp Ile Tyr Ala Gln Arg Met
        435                 440                 445
His Ala Phe Ile Thr Ser Leu Ser Ser Val Gly Ile Val Val Ser Asp
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cagggactgt gtcgggcttg gacctcacct gatcctctct cttagcgcga cccttcctct     240
gctccctgtc tcctctttct gccacttgtg cgctgcttcc gcgcactccc ggctccctag     300
cggcaggagg aggaaggcgc acagcgggtg gagagggtgc gccaaggaga ggtaacccct     360
tcgggagccc ggggaatccc ggccgccacc aggggccgtg ccaccgccct cgcgggacca     420
aagcttccgg cgtgtcccca actttgtggc gccctcaggc cgcggcgact gggttagag      479
atg cct tcc agc ggc aga gcg ctg ctg gac tcg ccg ctg gac agc ggc       527
Met Pro Ser Ser Gly Arg Ala Leu Leu Asp Ser Pro Leu Asp Ser Gly
 1               5                  10                  15

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Ser Leu Thr Ser Leu Asp Ser Ser Val Phe Cys Ser Glu Gly Glu Gly
            20                  25                  30

gag ccc ttg gcg ctc ggg gac tgc ttc acg gtc aac gtg ggc ggc agc       623
Glu Pro Leu Ala Leu Gly Asp Cys Phe Thr Val Asn Val Gly Gly Ser
        35                  40                  45

cgc ttc gtg ctc tcg cag cag gcg ctg tcc tgc ttc ccg cac acg cgc       671
Arg Phe Val Leu Ser Gln Gln Ala Leu Ser Cys Phe Pro His Thr Arg
    50                  55                  60

ctt ggc aag ctg gcc gtg gtg gtg gct tcc tac cgc cgc ccc ggg gcc       719
Leu Gly Lys Leu Ala Val Val Val Ala Ser Tyr Arg Arg Pro Gly Ala
 65                  70                  75                  80

ctg gcc gcc gtg ccc agc cct ctg gag ctt tgc gac gat gcc aac ccc       767
Leu Ala Ala Val Pro Ser Pro Leu Glu Leu Cys Asp Asp Ala Asn Pro
                 85                  90                  95
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gtg gac aac gag tac ttc ttc gac cgc agc tcg cag gcg ttc cga tat 815
Val Asp Asn Glu Tyr Phe Phe Asp Arg Ser Ser Gln Ala Phe Arg Tyr
100 105 110

gtc ctg cac tac tac cgc acc ggc cgc ctg cat gtc atg gag cag ctg 863
Val Leu His Tyr Tyr Arg Thr Gly Arg Leu His Val Met Glu Gln Leu
115 120 125

tgc gcg ctc tcc ttc ctg cag gag atc cag tac tgg ggc atc gat gag 911
Cys Ala Leu Ser Phe Leu Gln Glu Ile Gln Tyr Trp Gly Ile Asp Glu
130 135 140

ctc agc atc gat tcc tgc tgc agg gac aga tac ttc aga agg aaa gag 959
Leu Ser Ile Asp Ser Cys Cys Arg Asp Arg Tyr Phe Arg Arg Lys Glu
145 150 155 160

ctg agt gaa act tta gac ttc aag aag gac aca gaa gac cag gaa agt 1007
Leu Ser Glu Thr Leu Asp Phe Lys Lys Asp Thr Glu Asp Gln Glu Ser
165 170 175

caa cat gag agt gaa cag gac ttc tcc caa gga cct tgt ccc act gtt 1055
Gln His Glu Ser Glu Gln Asp Phe Ser Gln Gly Pro Cys Pro Thr Val
180 185 190

cgc cag aag ctc tgg aat atc ctg gag aaa cct gga tct tcc aca gct 1103
Arg Gln Lys Leu Trp Asn Ile Leu Glu Lys Pro Gly Ser Ser Thr Ala
195 200 205

gcc cgt atc ttt ggc gtc atc tcc att atc ttc gtg gtg gtg tcc atc 1151
Ala Arg Ile Phe Gly Val Ile Ser Ile Ile Phe Val Val Val Ser Ile
210 215 220

att aac atg gcc ctg atg tca gct gag tta agc tgg ctg gac ctg cag 1199
Ile Asn Met Ala Leu Met Ser Ala Glu Leu Ser Trp Leu Asp Leu Gln
225 230 235 240

ctg ctg gaa atc ctg gag tat gtg tgc att agc tgg ttc acc ggg gag 1247
Leu Leu Glu Ile Leu Glu Tyr Val Cys Ile Ser Trp Phe Thr Gly Glu
245 250 255

ttt gtc ctc cgc ttc ctg tgt gtg cgg gac agg tgt cgc ttc cta aga 1295
Phe Val Leu Arg Phe Leu Cys Val Arg Asp Arg Cys Arg Phe Leu Arg
260 265 270

aag gtg cca aac atc ata gac ctc ctt gcc atc ttg ccc ttc tac atc 1343
Lys Val Pro Asn Ile Ile Asp Leu Leu Ala Ile Leu Pro Phe Tyr Ile
275 280 285

act ctt ctg gta gag agc cta agt ggg agc cag acc acg cag gag ctg 1391
Thr Leu Leu Val Glu Ser Leu Ser Gly Ser Gln Thr Thr Gln Glu Leu
290 295 300

gag aac gtg ggg cgc att gtc cag gtg ttg agg ctg ctc agg gct ctg 1439
Glu Asn Val Gly Arg Ile Val Gln Val Leu Arg Leu Leu Arg Ala Leu
305 310 315 320

cgc atg cta aag ctg ggc aga cat tcc aca gga tta cgc tcc ctt ggg 1487
Arg Met Leu Lys Leu Gly Arg His Ser Thr Gly Leu Arg Ser Leu Gly
325 330 335

atg aca atc acc cag tgt tac gaa gaa gtc ggc cta ctg ctc cta ttt 1535
Met Thr Ile Thr Gln Cys Tyr Glu Glu Val Gly Leu Leu Leu Leu Phe
340 345 350

cta tcc gtg gga atc tct ata ttt tca act gta gaa tac ttt gct gag 1583
Leu Ser Val Gly Ile Ser Ile Phe Ser Thr Val Glu Tyr Phe Ala Glu
355 360 365

caa agc att cct gac aca acc ttc aca agt gtc cct tgt gca tgg tgg 1631
Gln Ser Ile Pro Asp Thr Thr Phe Thr Ser Val Pro Cys Ala Trp Trp
370 375 380

tgg gcc acc acc tct atg act act gtg gga tat ggg gac att aga cca 1679
Trp Ala Thr Thr Ser Met Thr Thr Val Gly Tyr Gly Asp Ile Arg Pro
385 390 395 400

gac acc acc aca ggc aaa atc gtg gcc ttc atg tgt ata tta tcg gga 1727
Asp Thr Thr Thr Gly Lys Ile Val Ala Phe Met Cys Ile Leu Ser Gly
405 410 415

att ctt gtc ttg gcc ttg cct att gct att att aac gat cgc ttc tct 1775
Ile Leu Val Leu Ala Leu Pro Ile Ala Ile Ile Asn Asp Arg Phe Ser
420 425 430

gct tgc tac ttc acc ttg aaa ctc aag gaa gca gct gtt aga cag cgt 1823
Ala Cys Tyr Phe Thr Leu Lys Leu Lys Glu Ala Ala Val Arg Gln Arg
435 440 445

gaa gcc cta aag aag ctt acc aag aat ata gcc act gac tca tat atc 1871
Glu Ala Leu Lys Lys Leu Thr Lys Asn Ile Ala Thr Asp Ser Tyr Ile
450 455 460

agt gtt aac ttg aga gat gtc tat gcc cgg agt atc atg gag atg ctg 1919
Ser Val Asn Leu Arg Asp Val Tyr Ala Arg Ser Ile Met Glu Met Leu
465 470 475 480

cga ctg aaa ggc aga gaa aga gca agt act agg agc agc ggg gga gat 1967
Arg Leu Lys Gly Arg Glu Arg Ala Ser Thr Arg Ser Ser Gly Gly Asp
485 490 495

gat ttc tgg t tttgaattaa ttttcaattt atttacaaaa gctatgtaca 2017
Asp Phe Trp

attaactaaa atgataaagc agtgatgtgg atttctgtat tctgatgatg agtctcttca 2077
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<213> H. sapiens

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35 40 45
Arg Phe Val Leu Ser Gln Gln Ala Leu Ser Cys Phe Pro His Thr Arg
50 55 60
Leu Gly Lys Leu Ala Val Val Val Ala Ser Tyr Arg Arg Pro Gly Ala
65 70 75 80
Leu Ala Ala Val Pro Ser Pro Leu Glu Leu Cys Asp Asp Ala Asn Pro
85 90 95
Val Asp Asn Glu Tyr Phe Phe Asp Arg Ser Ser Gln Ala Phe Arg Tyr
100 105 110
Val Leu His Tyr Tyr Arg Thr Gly Arg Leu His Val Met Glu Gln Leu
115 120 125
Cys Ala Leu Ser Phe Leu Gln Glu Ile Gln Tyr Trp Gly Ile Asp Glu
130 135 140
Leu Ser Ile Asp Ser Cys Cys Arg Asp Arg Tyr Phe Arg Arg Lys Glu
145 150 155 160
Leu Ser Glu Thr Leu Asp Phe Lys Lys Asp Thr Glu Asp Gln Glu Ser
165 170 175
Gln His Glu Ser Glu Gln Asp Phe Ser Gln Gly Pro Cys Pro Thr Val
180 185 190
Arg Gln Lys Leu Trp Asn Ile Leu Glu Lys Pro Gly Ser Ser Thr Ala
195 200 205
Ala Arg Ile Phe Gly Val Ile Ser Ile Ile Phe Val Val Val Ser Ile
210 215 220
Ile Asn Met Ala Leu Met Ser Ala Glu Leu Ser Trp Leu Asp Leu Gln
225 230 235 240
Leu Leu Glu Ile Leu Glu Tyr Val Cys Ile Ser Trp Phe Thr Gly Glu
245 250 255
Phe Val Leu Arg Phe Leu Cys Val Arg Asp Arg Cys Arg Phe Leu Arg
260 265 270
Lys Val Pro Asn Ile Ile Asp Leu Leu Ala Ile Leu Pro Phe Tyr Ile
275 280 285
Thr Leu Leu Val Glu Ser Leu Ser Gly Ser Gln Thr Thr Gln Glu Leu
290 295 300
Glu Asn Val Gly Arg Ile Val Gln Val Leu Arg Leu Leu Arg Ala Leu
305 310 315 320
Arg Met Leu Lys Leu Gly Arg His Ser Thr Gly Leu Arg Ser Leu Gly
325 330 335
Met Thr Ile Thr Gln Cys Tyr Glu Glu Val Gly Leu Leu Leu Leu Phe
340 345 350
Leu Ser Val Gly Ile Ser Ile Phe Ser Thr Val Glu Tyr Phe Ala Glu
355 360 365
Gln Ser Ile Pro Asp Thr Thr Phe Thr Ser Val Pro Cys Ala Trp Trp
370 375 380
Trp Ala Thr Thr Ser Met Thr Thr Val Gly Tyr Gly Asp Ile Arg Pro
385 390 395 400
Asp Thr Thr Thr Gly Lys Ile Val Ala Phe Met Cys Ile Leu Ser Gly
405 410 415
Ile Leu Val Leu Ala Leu Pro Ile Ala Ile Ile Asn Asp Arg Phe Ser

420 425 430
Ala Cys Tyr Phe Thr Leu Lys Leu Lys Glu Ala Ala Val Arg Gln Arg
435 440 445
Glu Ala Leu Lys Lys Leu Thr Lys Asn Ile Ala Thr Asp Ser Tyr Ile
450 455 460
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Arg Leu Lys Gly Arg Glu Arg Ala Ser Thr Arg Ser Ser Gly Gly Asp
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Asp Phe Trp

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cttggcctct ctagacaccc ccagtttcct tgtttgggtg gctcaaggtg tctccaagcc 180
cccaccatcc tggagacagc cacattctcc taaacgccac cctcactaag tctccctggg 240
cttggggagt ggcacg atg gcg gca ggc ctg gcc acg tgg ctg cct ttt gct 292
Met Ala Ala Gly Leu Ala Thr Trp Leu Pro Phe Ala
1 5 10

cgg gca gca gca gtg ggc tgg ctg ccc ccg gcc cag caa ccc ctg ccc 340
Arg Ala Ala Ala Val Gly Trp Leu Pro Pro Ala Gln Gln Pro Leu Pro
15 20 25

ccg gca ccg ggg gtg aag gca tct cga gga gat grg gtt ctg gtg gtg 388
Pro Ala Pro Gly Val Lys Ala Ser Arg Gly Asp Xaa Val Leu Val Val
30 35 40

aac gtg agc gga cgg cgc ttt gag act tgg aag aat acg ctg gac cgc 436
Asn Val Ser Gly Arg Arg Phe Glu Thr Trp Lys Asn Thr Leu Asp Arg
45 50 55 60

tac cca gac acc ttg ctg ggc agc tcg gag aag gaa ttc ttc tac gat 484
Tyr Pro Asp Thr Leu Leu Gly Ser Ser Glu Lys Glu Phe Phe Tyr Asp
65 70 75

gct gac tca ggc gag tac ttc ttc gat cgc gac cct gac atg ttc cgc 532
Ala Asp Ser Gly Glu Tyr Phe Phe Asp Arg Asp Pro Asp Met Phe Arg
80 85 90

cat gtg ctg aac ttc tac cga acg ggg cgg ctg cat tgc cca cgg cag 580
His Val Leu Asn Phe Tyr Arg Thr Gly Arg Leu His Cys Pro Arg Gln
95 100 105

gag tgc atc cag gcc ttc gac gaa gag ctg gct ttc tac ggc ctg gtt 628
Glu Cys Ile Gln Ala Phe Asp Glu Glu Leu Ala Phe Tyr Gly Leu Val
110 115 120

ccc gag cta gtc ggt gac tgc tgc ctt gaa gag tat cgg gac cga aag 676
Pro Glu Leu Val Gly Asp Cys Cys Leu Glu Glu Tyr Arg Asp Arg Lys

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125                 130                 135                 140

aag gag aat gcc gag cgc ctg gca gag gat gag gag gca gag cag gcc      724
Lys Glu Asn Ala Glu Arg Leu Ala Glu Asp Glu Glu Ala Glu Gln Ala
                145                 150                 155

ggg gac ggc cca gcc ctg cca gca ggc agc tcc ctg cgg cag cgg ctc      772
Gly Asp Gly Pro Ala Leu Pro Ala Gly Ser Ser Leu Arg Gln Arg Leu
            160                 165                 170

tgg cgg gcc ttc gag aat cca cac acg agc acc gca gcc ctc gtt ttc      820
Trp Arg Ala Phe Glu Asn Pro His Thr Ser Thr Ala Ala Leu Val Phe
        175                 180                 185

tac tat gtg acc ggc ttc ttc atc gcc gtg tcg gtc atc gcc aat gtg      868
Tyr Tyr Val Thr Gly Phe Phe Ile Ala Val Ser Val Ile Ala Asn Val
    190                 195                 200

gtg gag acc atc cca tgc cgc ggc tct gca cgc agg tcc tca agg gag      916
Val Glu Thr Ile Pro Cys Arg Gly Ser Ala Arg Arg Ser Ser Arg Glu
205                 210                 215                 220

cag ccc tgt ggc gaa cgc ttc cca cag gcc ttt ttc tgc atg gac aca      964
Gln Pro Cys Gly Glu Arg Phe Pro Gln Ala Phe Phe Cys Met Asp Thr
                225                 230                 235

gcc tgt gta ctc ata ttc aca ggt gaa tac ctc ctg cgg ctg ttt gcc     1012
Ala Cys Val Leu Ile Phe Thr Gly Glu Tyr Leu Leu Arg Leu Phe Ala
            240                 245                 250

gcc ccc agc cgt tgc cgc ttc ctg cgg agt gtc atg agc ctc atc gac     1060
Ala Pro Ser Arg Cys Arg Phe Leu Arg Ser Val Met Ser Leu Ile Asp
        255                 260                 265

gtg gtg gcc atc ctg ccc tac tac att ggg ctt ttg gtg ccc aag aac     1108
Val Val Ala Ile Leu Pro Tyr Tyr Ile Gly Leu Leu Val Pro Lys Asn
    270                 275                 280

gac gat gtc tct ggc gcc ttt gtc acc ctg cgt gtg ttc cgg gtg ttt     1156
Asp Asp Val Ser Gly Ala Phe Val Thr Leu Arg Val Phe Arg Val Phe
285                 290                 295                 300

cgc atc ttc aag ttc tcc agg cac tca cag ggc ttg agg att ctg ggc     1204
Arg Ile Phe Lys Phe Ser Arg His Ser Gln Gly Leu Arg Ile Leu Gly
                305                 310                 315

tac aca ctc aag agc tgt gcc tct gag ctg ggc ttt ctc ctc ttt tcc     1252
Tyr Thr Leu Lys Ser Cys Ala Ser Glu Leu Gly Phe Leu Leu Phe Ser
            320                 325                 330

cta acc atg gcc atc atc atc ttt gcc act gtc atg ttt tat gct gag     1300
Leu Thr Met Ala Ile Ile Ile Phe Ala Thr Val Met Phe Tyr Ala Glu
        335                 340                 345

aag ggc aca aac aag acc aac ttt aca agc atc cct gcg gcc ttc tgg     1348
Lys Gly Thr Asn Lys Thr Asn Phe Thr Ser Ile Pro Ala Ala Phe Trp
    350                 355                 360

tat acc att gtc acc atg acc acg ctt ggc tac gga gac atg gtg ccc     1396
Tyr Thr Ile Val Thr Met Thr Thr Leu Gly Tyr Gly Asp Met Val Pro
365                 370                 375                 380
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agc acc att gct ggc aag att ttc ggg tcc atc tgc tca ctc agt ggc     1444
Ser Thr Ile Ala Gly Lys Ile Phe Gly Ser Ile Cys Ser Leu Ser Gly
                385                 390                 395

gtc ttg gtc att gcc ctg cct gtg cca gtc att gtg tcc aac ttt agc     1492
Val Leu Val Ile Ala Leu Pro Val Pro Val Ile Val Ser Asn Phe Ser
            400                 405                 410

cgc atc tac cac cag aac cag cgg gct gac aag cgc cga gca cag cag     1540
Arg Ile Tyr His Gln Asn Gln Arg Ala Asp Lys Arg Arg Ala Gln Gln
        415                 420                 425

aag gtg cgc ttg gca agg atc cga ttg gca aag agt ggt acc acc aat     1588
Lys Val Arg Leu Ala Arg Ile Arg Leu Ala Lys Ser Gly Thr Thr Asn
    430                 435                 440

gcc ttc ctg cag tac aag cag aat ggg ggc ctt gag gac agc ggc agt     1636
Ala Phe Leu Gln Tyr Lys Gln Asn Gly Gly Leu Glu Asp Ser Gly Ser
445                 450                 455                 460

ggc gag gaa cag gct ctt tgt gtc agg aac cgt tct gcc ttt gaa cag     1684
Gly Glu Glu Gln Ala Leu Cys Val Arg Asn Arg Ser Ala Phe Glu Gln
                465                 470                 475

caa cat cac cac ttg ctg cac tgt cta gag aag aca acg tgc cat gag     1732
Gln His His His Leu Leu His Cys Leu Glu Lys Thr Thr Cys His Glu
            480                 485                 490

ttc aca gat gag ctc acc ttc agt gaa gcc ctg gga gcc gtc tcg ccg     1780
Phe Thr Asp Glu Leu Thr Phe Ser Glu Ala Leu Gly Ala Val Ser Pro
        495                 500                 505

ggt ggc cgc acc agc cgt agc acc tct gtg tct tcc cag cca gtg gga     1828
Gly Gly Arg Thr Ser Arg Ser Thr Ser Val Ser Ser Gln Pro Val Gly
    510                 515                 520

ccc gga agc ctg ctg tct tct tgc tgc cct cgc agg gcc aag cgc cgc     1876
Pro Gly Ser Leu Leu Ser Ser Cys Cys Pro Arg Arg Ala Lys Arg Arg
525                 530                 535                 540

gcc atc cgc ctt gcc aac tcc act gcc tca gtc agc cgt ggc agc atg     1924
Ala Ile Arg Leu Ala Asn Ser Thr Ala Ser Val Ser Arg Gly Ser Met
                545                 550                 555

cag gag ctg gac atg ctg gca ggg ctg cgc agg agc cat gcc cct cag     1972
Gln Glu Leu Asp Met Leu Ala Gly Leu Arg Arg Ser His Ala Pro Gln
            560                 565                 570

agc cgc tcc agc ctc aat gcc aag ccc cat gac agc ctt gac ctg aac     2020
Ser Arg Ser Ser Leu Asn Ala Lys Pro His Asp Ser Leu Asp Leu Asn
        575                 580                 585

tgc gac agc cgg gac ttc gtg gct gcc att atc agc atc cct acc cct     2068
Cys Asp Ser Arg Asp Phe Val Ala Ala Ile Ile Ser Ile Pro Thr Pro
    590                 595                 600

cct gcc aac acc cca gat gag agc caa cct tcc tcc cct ggc ggc ggt     2116
Pro Ala Asn Thr Pro Asp Glu Ser Gln Pro Ser Ser Pro Gly Gly Gly
605                 610                 615                 620
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ggc agg gcc ggc agc acc ctc agg aac tcc agc ctg ggt acc cct tgc      2164
Gly Arg Ala Gly Ser Thr Leu Arg Asn Ser Ser Leu Gly Thr Pro Cys
                625                     630                 635

ctc ttc ccc gag act gtc aag atc tca tcc c tgtgaggggt aggcctgctg      2215
Leu Phe Pro Glu Thr Val Lys Ile Ser Ser
            640                     645

attcagaggg tcctcttcat ttttgggaac tcctttccaa agccatattt ttgggaggca     2275
gagaggggca ggcttgggca ccccttctgc ccccccact gagaactatg caatggagtt      2335
tcatgaaatg gtccacatag tggggaagta gccaggaaat gagaaacttc ctcccacccc     2395
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Val Lys Ala Ser Arg Gly Asp Xaa Val Leu Val Val Asn Val Ser Gly
        35                  40                  45
Arg Arg Phe Glu Thr Trp Lys Asn Thr Leu Asp Arg Tyr Pro Asp Thr
    50                  55                  60
Leu Leu Gly Ser Ser Glu Lys Glu Phe Phe Tyr Asp Ala Asp Ser Gly
65                  70                  75                  80
Glu Tyr Phe Phe Asp Arg Asp Pro Asp Met Phe Arg His Val Leu Asn
                85                  90                  95
Phe Tyr Arg Thr Gly Arg Leu His Cys Pro Arg Gln Glu Cys Ile Gln
            100                 105                 110
Ala Phe Asp Glu Glu Leu Ala Phe Tyr Gly Leu Val Pro Glu Leu Val
        115                 120                 125
Gly Asp Cys Cys Leu Glu Glu Tyr Arg Asp Arg Lys Lys Glu Asn Ala
    130                 135                 140
Glu Arg Leu Ala Glu Asp Glu Glu Ala Glu Gln Ala Gly Asp Gly Pro
145                 150                 155                 160
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Ala Leu Pro Ala Gly Ser Ser Leu Arg Gln Arg Leu Trp Arg Ala Phe
                165                 170                 175
Glu Asn Pro His Thr Ser Thr Ala Ala Leu Val Phe Tyr Tyr Val Thr
            180                 185                 190
Gly Phe Phe Ile Ala Val Ser Val Ile Ala Asn Val Val Glu Thr Ile
        195                 200                 205
Pro Cys Arg Gly Ser Ala Arg Arg Ser Ser Arg Glu Gln Pro Cys Gly
    210                 215                 220
Glu Arg Phe Pro Gln Ala Phe Phe Cys Met Asp Thr Ala Cys Val Leu
225                 230                 235                 240
Ile Phe Thr Gly Glu Tyr Leu Leu Arg Leu Phe Ala Ala Pro Ser Arg
                245                 250                 255
Cys Arg Phe Leu Arg Ser Val Met Ser Leu Ile Asp Val Val Ala Ile
            260                 265                 270
Leu Pro Tyr Tyr Ile Gly Leu Leu Val Pro Lys Asn Asp Asp Val Ser
        275                 280                 285
Gly Ala Phe Val Thr Leu Arg Val Phe Arg Val Phe Arg Ile Phe Lys
    290                 295                 300
Phe Ser Arg His Ser Gln Gly Leu Arg Ile Leu Gly Tyr Thr Leu Lys
305                 310                 315                 320
Ser Cys Ala Ser Glu Leu Gly Phe Leu Leu Phe Ser Leu Thr Met Ala
                325                 330                 335
Ile Ile Ile Phe Ala Thr Val Met Phe Tyr Ala Glu Lys Gly Thr Asn
            340                 345                 350
Lys Thr Asn Phe Thr Ser Ile Pro Ala Ala Phe Trp Tyr Thr Ile Val
        355                 360                 365
Thr Met Thr Thr Leu Gly Tyr Gly Asp Met Val Pro Ser Thr Ile Ala
    370                 375                 380
Gly Lys Ile Phe Gly Ser Ile Cys Ser Leu Ser Gly Val Leu Val Ile
385                 390                 395                 400
Ala Leu Pro Val Pro Val Ile Val Ser Asn Phe Ser Arg Ile Tyr His
                405                 410                 415
Gln Asn Gln Arg Ala Asp Lys Arg Arg Ala Gln Gln Lys Val Arg Leu
            420                 425                 430
Ala Arg Ile Arg Leu Ala Lys Ser Gly Thr Thr Asn Ala Phe Leu Gln
        435                 440                 445
Tyr Lys Gln Asn Gly Gly Leu Glu Asp Ser Gly Ser Gly Glu Glu Gln
    450                 455                 460
Ala Leu Cys Val Arg Asn Arg Ser Ala Phe Glu Gln Gln His His His
465                 470                 475                 480
Leu Leu His Cys Leu Glu Lys Thr Thr Cys His Glu Phe Thr Asp Glu
                485                 490                 495
Leu Thr Phe Ser Glu Ala Leu Gly Ala Val Ser Pro Gly Gly Arg Thr
            500                 505                 510
Ser Arg Ser Thr Ser Val Ser Ser Gln Pro Val Gly Pro Gly Ser Leu
        515                 520                 525
Leu Ser Ser Cys Cys Pro Arg Arg Ala Lys Arg Arg Ala Ile Arg Leu
    530                 535                 540
Ala Asn Ser Thr Ala Ser Val Ser Arg Gly Ser Met Gln Glu Leu Asp
545                 550                 555                 560
Met Leu Ala Gly Leu Arg Arg Ser His Ala Pro Gln Ser Arg Ser Ser
                565                 570                 575
Leu Asn Ala Lys Pro His Asp Ser Leu Asp Leu Asn Cys Asp Ser Arg
            580                 585                 590
Asp Phe Val Ala Ala Ile Ile Ser Ile Pro Thr Pro Pro Ala Asn Thr
        595                 600                 605
Pro Asp Glu Ser Gln Pro Ser Ser Pro Gly Gly Gly Gly Arg Ala Gly
    610                 615                 620
Ser Thr Leu Arg Asn Ser Ser Leu Gly Thr Pro Cys Leu Phe Pro Glu
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Thr Val Lys Ile Ser Ser
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645

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tgactcttaa ttacatcaca cctgtgtcga cactctctgg gaaaagactg aagaaataat     180
cttttcaaga agcagaaagc tcctgcatac ataggctgat acgccaccta ctgcaaaacc     240
gagctgacag cgcaggcgat gctgccagcg tttccattcc atcaccaggc tggggctgaa     300
taaaggcgtg cttgtgtggt agtgtctctt tttaaaaaat ctcaaagcca agaagaacaa     360
gctgaaatag catcttcaaa aa atg gag cgt aaa ata aac aga aga gaa aaa     412
                         Met Glu Arg Lys Ile Asn Arg Arg Glu Lys
                          1               5                  10

gaa aag gag tat gaa ggg aaa cac aac agc ctg gaa gat act gat caa     460
Glu Lys Glu Tyr Glu Gly Lys His Asn Ser Leu Glu Asp Thr Asp Gln
                15                  20                  25

gga aag aac tgc aaa tcc aca ctg atg acc ctc aac gtt ggt gga tat     508
Gly Lys Asn Cys Lys Ser Thr Leu Met Thr Leu Asn Val Gly Gly Tyr
            30                  35                  40

tta tac att act caa aaa caa aca ctg acc aag tac cca gac act ttc     556
Leu Tyr Ile Thr Gln Lys Gln Thr Leu Thr Lys Tyr Pro Asp Thr Phe
        45                  50                  55

ctt gaa ggt ata gta aat gga aaa atc ctc tgc ccg ttt gat gct gat     604
Leu Glu Gly Ile Val Asn Gly Lys Ile Leu Cys Pro Phe Asp Ala Asp
    60                  65                  70

ggt cat tat ttc ata gac agg gat ggt ctc ctc ttc agg cat gtc cta     652
Gly His Tyr Phe Ile Asp Arg Asp Gly Leu Leu Phe Arg His Val Leu
75                  80                  85                  90

aac ttc cta cga aat gga gaa ctt cta ttg ccc gaa ggg ttt cga gaa     700
Asn Phe Leu Arg Asn Gly Glu Leu Leu Leu Pro Glu Gly Phe Arg Glu
                95                  100                 105

aat caa ctt ctt gca caa gaa gca gaa ttc ttt cag ctc aag gga ctg     748
Asn Gln Leu Leu Ala Gln Glu Ala Glu Phe Phe Gln Leu Lys Gly Leu
            110                 115                 120

gca gag gaa gtg aaa tcc agg tgg gag aaa gaa cag cta aca ccc aga     796
Ala Glu Glu Val Lys Ser Arg Trp Glu Lys Glu Gln Leu Thr Pro Arg
        125                 130                 135

gag act act ttc ttg gaa ata aca gat aac cac gat cgt tca caa gga     844
Glu Thr Thr Phe Leu Glu Ile Thr Asp Asn His Asp Arg Ser Gln Gly
    140                 145                 150

tta aga atc ttc tgt aat gct cct gat ttc ata tca aaa ata aag tct     892
Leu Arg Ile Phe Cys Asn Ala Pro Asp Phe Ile Ser Lys Ile Lys Ser
```

155 160 165 170

cgc att gtt ctg gtg tcc aaa agc agg ctg gat gga ttt cca gag gag 940
Arg Ile Val Leu Val Ser Lys Ser Arg Leu Asp Gly Phe Pro Glu Glu
175 180 185

ttt tca ata tcg tca aat atc atc caa ttt aaa tac ttc ata aag tct 988
Phe Ser Ile Ser Ser Asn Ile Ile Gln Phe Lys Tyr Phe Ile Lys Ser
190 195 200

gaa aat ggc act cga ctt gta cta aag gaa gac aac acc ttt gtc tgt 1036
Glu Asn Gly Thr Arg Leu Val Leu Lys Glu Asp Asn Thr Phe Val Cys
205 210 215

acc ttg gaa act ctt aag ttt gag gct atc atg atg gct tta aag tgt 1084
Thr Leu Glu Thr Leu Lys Phe Glu Ala Ile Met Met Ala Leu Lys Cys
220 225 230

ggc ttt aga ctg ctg acc agc ctg gat tgt tcc aaa ggg tca att gtt 1132
Gly Phe Arg Leu Leu Thr Ser Leu Asp Cys Ser Lys Gly Ser Ile Val
235 240 245 250

cac agc gat gca ctt cat ttt atc a agtaattacc tgtgtcacga 1177
His Ser Asp Ala Leu His Phe Ile
255

acaaaggcaa caagcatgca gccagcaagc ttcggaaaac cacagcatca aagacatccc 1237
aaataacatg cccagctagc tctgtactac agagccctgc tactaatcaa ttactgtgag 1297
ctaacggtat gtaaattcta tcgctaaaga tgtccttcct ctggggtgtt cctactgatc 1357
agactcttcc acctaaaatg aaaacagtaa ccttctatat actgtaaata aagactgaaa 1417
gcttttgcta tttatttgtc cttaagctgt ctttcaattc agattgtctt gggtatttgc 1477
acaaaaagaa gcatgtacat tatctatcgt tcatttaagt aaatggtaat aaaatatttt 1537
aaggggctat taatatttaa aatccttttc tactatggca aaaatctaca gagaaactga 1597
actggcaaaa ttaactacct ggagcaaaac agatgtgcag atctaactaa aacagagcta 1657
tagtgaaaca aaatgagatt gtaagaagac attaaagcta ttgatttgat ttttccatag 1717
caagcaccaa aagcttatat tcacagttcc tgtgtttcat attagactta tagctgaatt 1777
ggtattttgc tgaaaattcc tagaaaactg cttgatgaca ataaaaagta aataaaagca 1837
ctgctacctt caaaaaaaaa aaaaa 1862

<210> 12
<211> 258
<212> PRT
<213> H. sapiens

<400> 12
Met Glu Arg Lys Ile Asn Arg Arg Glu Lys Glu Lys Glu Tyr Glu Gly
1 5 10 15
Lys His Asn Ser Leu Glu Asp Thr Asp Gln Gly Lys Asn Cys Lys Ser
20 25 30
Thr Leu Met Thr Leu Asn Val Gly Gly Tyr Leu Tyr Ile Thr Gln Lys
35 40 45
Gln Thr Leu Thr Lys Tyr Pro Asp Thr Phe Leu Glu Gly Ile Val Asn
50 55 60
Gly Lys Ile Leu Cys Pro Phe Asp Ala Asp Gly His Tyr Phe Ile Asp
65 70 75 80
Arg Asp Gly Leu Leu Phe Arg His Val Leu Asn Phe Leu Arg Asn Gly
85 90 95
Glu Leu Leu Leu Pro Glu Gly Phe Arg Glu Asn Gln Leu Leu Ala Gln
100 105 110
Glu Ala Glu Phe Phe Gln Leu Lys Gly Leu Ala Glu Glu Val Lys Ser
115 120 125

```
Arg Trp Glu Lys Glu Gln Leu Thr Pro Arg Glu Thr Thr Phe Leu Glu
    130                 135                 140
Ile Thr Asp Asn His Asp Arg Ser Gln Gly Leu Arg Ile Phe Cys Asn
145                 150                 155                 160
Ala Pro Asp Phe Ile Ser Lys Ile Lys Ser Arg Ile Val Leu Val Ser
                165                 170                 175
Lys Ser Arg Leu Asp Gly Phe Pro Glu Glu Phe Ser Ile Ser Ser Asn
            180                 185                 190
Ile Ile Gln Phe Lys Tyr Phe Ile Lys Ser Glu Asn Gly Thr Arg Leu
        195                 200                 205
Val Leu Lys Glu Asp Asn Thr Phe Val Cys Thr Leu Glu Thr Leu Lys
    210                 215                 220
Phe Glu Ala Ile Met Met Ala Leu Lys Cys Gly Phe Arg Leu Leu Thr
225                 230                 235                 240
Ser Leu Asp Cys Ser Lys Gly Ser Ile Val His Ser Asp Ala Leu His
                245                 250                 255
Phe Ile
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<210> 13
<211> 1877
<212> DNA
<213> H. sapiens

<220>
<221> CDS
<222> (322)...(1090)
<223> K+Hnov27

<400> 13

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gtcgggcccg acgtgaaatc cgaggctgcg cccaagcgcg ccctgtacga gtctgtgttc     120
gggtcggggg aaatctgcgg ccccacttcc cccaaaagac tttgtatccg cccctcggag     180
cctgtggatg cggtggtggt ggtttccgtg aaacacgacc ccctgcctct tcttccagaa     240
gccaatgggc acagaagcac caattctccc acaatagttt cacctgctat tgtttccccc     300
acccaggaca gtcggcccaa t atg tca aga cct ctg atc act aga tcc cct       351
                        Met Ser Arg Pro Leu Ile Thr Arg Ser Pro
                        1               5                   10

gca tct cca ctg awc aac caa ggc atc cct act cca gca caa ctc aca       399
Ala Ser Pro Leu Xaa Asn Gln Gly Ile Pro Thr Pro Ala Gln Leu Thr
                15                  20                  25

aaa tcc aat gcg cct gtc cac att gat gtg ggc ggc cac atg tac acc       447
Lys Ser Asn Ala Pro Val His Ile Asp Val Gly Gly His Met Tyr Thr
            30                  35                  40

agc agc ctg gcc acc ctc acc aaa tac cct gaa tcc aga atc gga aga       495
Ser Ser Leu Ala Thr Leu Thr Lys Tyr Pro Glu Ser Arg Ile Gly Arg
        45                  50                  55

ctt ttt gat ggt aca gag ccc att gtt ttg gac agt ctc aaa cag cac       543
Leu Phe Asp Gly Thr Glu Pro Ile Val Leu Asp Ser Leu Lys Gln His
    60                  65                  70

tat ttc att gac aga gat gga cag atg ttc aga tat atc ttg aat ttt       591
Tyr Phe Ile Asp Arg Asp Gly Gln Met Phe Arg Tyr Ile Leu Asn Phe
75                  80                  85                  90

cta cga aca tcc aaa ctc ctc att cct gat gat ttc aag gac tac act       639
Leu Arg Thr Ser Lys Leu Leu Ile Pro Asp Asp Phe Lys Asp Tyr Thr
```

95 100 105

ttg tta tat gaa gag gca aaa tat ttt cag ctt cag ccc atg ttg ttg 687
Leu Leu Tyr Glu Glu Ala Lys Tyr Phe Gln Leu Gln Pro Met Leu Leu
110 115 120

gag atg gaa aga tgg aag cag gac aga gaa act ggt cga ttt tca agg 735
Glu Met Glu Arg Trp Lys Gln Asp Arg Glu Thr Gly Arg Phe Ser Arg
125 130 135

ccc tgt gag tgc ctc gtc gtg cgt gtg gcc cca gac ctc gga gaa agg 783
Pro Cys Glu Cys Leu Val Val Arg Val Ala Pro Asp Leu Gly Glu Arg
140 145 150

atc acg cta agc ggt gac aaa tcc ttg ata gaa gaa gta ttt cca gag 831
Ile Thr Leu Ser Gly Asp Lys Ser Leu Ile Glu Glu Val Phe Pro Glu
155 160 165 170

atc ggc gac gtg atg tgt aac tct gtc aat gca ggc tgg aat cac gac 879
Ile Gly Asp Val Met Cys Asn Ser Val Asn Ala Gly Trp Asn His Asp
175 180 185

tcg acg cac gtc atc agg ttt cca cta aat ggc tac tgt cac ctc aac 927
Ser Thr His Val Ile Arg Phe Pro Leu Asn Gly Tyr Cys His Leu Asn
190 195 200

tca gtc cag gtc ctc gag agg ttg cag caa aga gga ttt gaa atc gtg 975
Ser Val Gln Val Leu Glu Arg Leu Gln Gln Arg Gly Phe Glu Ile Val
205 210 215

ggc tcc tgt ggg gga gga gta gac tcg tcc cag ttc agc gaa tac gtc 1023
Gly Ser Cys Gly Gly Gly Val Asp Ser Ser Gln Phe Ser Glu Tyr Val
220 225 230

ctt cgg cgg gaa ctg agg cgg acg ccc cgt gta ccc tcc gtc atc cgg 1071
Leu Arg Arg Glu Leu Arg Arg Thr Pro Arg Val Pro Ser Val Ile Arg
235 240 245 250

ata aag caa gag cct ctg g actaaatgga catatttctt atgcaaaaag 1120
Ile Lys Gln Glu Pro Leu
255

gaaaacacac acaaccaata actcaaacaa aaaagggaca tttatgtgca gttgggacag 1180
caaaccaagt cctggacgta aaattgaata aaagacacat ttatatccaa tagagaccac 1240
acctgtattc atatgggaac aattggaata gtgatatcct caaggtgtaa aaaatatata 1300
aatatatata tatatgtcaa aaggtaggaa atgcaaaaaa gaaaaaaaaa aaaggtgaca 1360
gccgcagttg gtgctgtgat ggccgtgaag tgtcctgggc ctcccgaggc ctctgacaaa 1420
taaacaagcc atgagtggtg aggacacagt ctccttacag tttccattgc caacaacagc 1480
catccatatt tctttttttcc tttgtctttc tttttccttt tttttaaaa aaacaaaaca 1540
aacaaaacac cttgaatcaa gtttgtttgt atatggaggt tccacgtctt tctttaggca 1600
gggaccaggc aggacttcag aaaaaccctc atgagcacat tgcaaagatg ttagacatga 1660
aattttaaat gtagtttgta cagaagtcac actttttttgt ccacctcaca gatgtgaact 1720
ttactttgtt ttaaaactga tcagttttgc caaggggcca gaattattcc ttgttagaat 1780
tgctccagtt caagtctgct gctttcctac aatttttcaa attttataat gtattaaata 1840
caataaactc tgtttaaaaa ataaaaaaaa aaaaaaa 1877

<210> 14
<211> 256
<212> PRT
<213> H. sapiens

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<220>
<221> VARIANT
<222> (1)...(256)
<223> Xaa = Any Amino Acid

<400> 14
Met Ser Arg Pro Leu Ile Thr Arg Ser Pro Ala Ser Pro Leu Xaa Asn
 1               5                  10                  15
Gln Gly Ile Pro Thr Pro Ala Gln Leu Thr Lys Ser Asn Ala Pro Val
            20                  25                  30
His Ile Asp Val Gly Gly His Met Tyr Thr Ser Ser Leu Ala Thr Leu
        35                  40                  45
Thr Lys Tyr Pro Glu Ser Arg Ile Gly Arg Leu Phe Asp Gly Thr Glu
    50                  55                  60
Pro Ile Val Leu Asp Ser Leu Lys Gln His Tyr Phe Ile Asp Arg Asp
65                  70                  75                  80
Gly Gln Met Phe Arg Tyr Ile Leu Asn Phe Leu Arg Thr Ser Lys Leu
                85                  90                  95
Leu Ile Pro Asp Asp Phe Lys Asp Tyr Thr Leu Leu Tyr Glu Glu Ala
            100                 105                 110
Lys Tyr Phe Gln Leu Gln Pro Met Leu Leu Glu Met Glu Arg Trp Lys
        115                 120                 125
Gln Asp Arg Glu Thr Gly Arg Phe Ser Arg Pro Cys Glu Cys Leu Val
    130                 135                 140
Val Arg Val Ala Pro Asp Leu Gly Glu Arg Ile Thr Leu Ser Gly Asp
145                 150                 155                 160
Lys Ser Leu Ile Glu Glu Val Phe Pro Glu Ile Gly Asp Val Met Cys
                165                 170                 175
Asn Ser Val Asn Ala Gly Trp Asn His Asp Ser Thr His Val Ile Arg
            180                 185                 190
Phe Pro Leu Asn Gly Tyr Cys His Leu Asn Ser Val Gln Val Leu Glu
        195                 200                 205
Arg Leu Gln Gln Arg Gly Phe Glu Ile Val Gly Ser Cys Gly Gly Gly
    210                 215                 220
Val Asp Ser Ser Gln Phe Ser Glu Tyr Val Leu Arg Arg Glu Leu Arg
225                 230                 235                 240
Arg Thr Pro Arg Val Pro Ser Val Ile Arg Ile Lys Gln Glu Pro Leu
                245                 250                 255

<210> 15
<211> 923
<212> DNA
<213> H. sapiens

<220>
<221> CDS
<222> (165)...(756)
<223> K+Hnov2

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gcgtggtggc aggtgcctgt agccccagct acttgggagg ctgaggcagg agaatagctt      60
gaacccgggc ggcgaaggtt gagtgagccg agattgcacc actgcactcc agcctgggcg     120
acagagcgag actccatctc aaaaaaaaga gtagttatgg ccac atg gcc cca cta      176
                                                 Met Ala Pro Leu
                                                  1

tcg cca ggc gga aag gcc ttc tgc atg gtc tat gca gcc ctg ggg ctg       224
Ser Pro Gly Gly Lys Ala Phe Cys Met Val Tyr Ala Ala Leu Gly Leu
 5                  10                  15                  20

cca gcc tcc tta gct ctc gtg gcc acc ctg cgc cat tgc ctg ctg cct       272
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Pro Ala Ser Leu Ala Leu Val Ala Thr Leu Arg His Cys Leu Leu Pro
                25                  30                  35

gtg ctc agc cgc cca cgt gcc tgg gta gcg gtc cac tgg cag ctg tca     320
Val Leu Ser Arg Pro Arg Ala Trp Val Ala Val His Trp Gln Leu Ser
            40                  45                  50

ccg gcc agg gct gcg ctg ctg cag gca gtt gca ctg gga ctg ctg gtg     368
Pro Ala Arg Ala Ala Leu Leu Gln Ala Val Ala Leu Gly Leu Leu Val
        55                  60                  65

gcc agc agc ttt gtg ctg ctg cca gcg ctg gtg ctg tgg ggc ctt cag     416
Ala Ser Ser Phe Val Leu Leu Pro Ala Leu Val Leu Trp Gly Leu Gln
    70                  75                  80

ggc gac tgc agc ctg ctg ggg gcc gtc tac ttc tgc ttc agc tcg ctc     464
Gly Asp Cys Ser Leu Leu Gly Ala Val Tyr Phe Cys Phe Ser Ser Leu
85                  90                  95                  100

agc acc att ggc ctg gag gac ttg ctg ccc ggc cgc ggc cgc agc ctg     512
Ser Thr Ile Gly Leu Glu Asp Leu Leu Pro Gly Arg Gly Arg Ser Leu
                105                 110                 115

cac ccc gtg att tac cac ctg ggc cag ctc gca ctt ctt ggt tac ttg     560
His Pro Val Ile Tyr His Leu Gly Gln Leu Ala Leu Leu Gly Tyr Leu
            120                 125                 130

ctt cta gga ctc ttg gcc atg ctg ctg gca gtg gag acc ttc tct gag     608
Leu Leu Gly Leu Leu Ala Met Leu Leu Ala Val Glu Thr Phe Ser Glu
        135                 140                 145

ctg ccg cag gtc cgt gcc atg ggg aag ttc ttc aga ccc agt ggt cct     656
Leu Pro Gln Val Arg Ala Met Gly Lys Phe Phe Arg Pro Ser Gly Pro
    150                 155                 160

gtg act gct gag gac caa ggt ggc atc cta ggg cag gat gaa ctg gct     704
Val Thr Ala Glu Asp Gln Gly Gly Ile Leu Gly Gln Asp Glu Leu Ala
165                 170                 175                 180

ctg agc acc ctg ccg ccc gcg gcc cca gct tca gga caa gcc cct gct     752
Leu Ser Thr Leu Pro Pro Ala Ala Pro Ala Ser Gly Gln Ala Pro Ala
                185                 190                 195

tgc t gaagcgtcag gtgaccgagt tcagctccgt aaggtggcgg cacctgagga        806
Cys

ggaagcagcc aggagtggct ggggaagaat ctggagatgg agccgcggtg agggtgggcg   866
ggaggcctca ggggatactg ttaatcataa aaaaaaaaaa aaaaaaaaaa aaaaaaa      923

      <210> 16
      <211> 197
      <212> PRT
      <213> H. sapiens

      <400> 16
Met Ala Pro Leu Ser Pro Gly Gly Lys Ala Phe Cys Met Val Tyr Ala
 1               5                  10                  15
Ala Leu Gly Leu Pro Ala Ser Leu Ala Leu Val Ala Thr Leu Arg His
            20                  25                  30
Cys Leu Leu Pro Val Leu Ser Arg Pro Arg Ala Trp Val Ala Val His
```

```
        35                                      40                                      45
Trp Gln Leu Ser Pro Ala Arg Ala Ala Leu Leu Gln Ala Val Ala Leu
    50                  55                  60
Gly Leu Leu Val Ala Ser Ser Phe Val Leu Leu Pro Ala Leu Val Leu
65                  70                  75                  80
Trp Gly Leu Gln Gly Asp Cys Ser Leu Leu Gly Ala Val Tyr Phe Cys
                85                  90                  95
Phe Ser Ser Leu Ser Thr Ile Gly Leu Glu Asp Leu Leu Pro Gly Arg
            100                 105                 110
Gly Arg Ser Leu His Pro Val Ile Tyr His Leu Gly Gln Leu Ala Leu
        115                 120                 125
Leu Gly Tyr Leu Leu Leu Gly Leu Leu Ala Met Leu Leu Ala Val Glu
    130                 135                 140
Thr Phe Ser Glu Leu Pro Gln Val Arg Ala Met Gly Lys Phe Phe Arg
145                 150                 155                 160
Pro Ser Gly Pro Val Thr Ala Glu Asp Gln Gly Gly Ile Leu Gly Gln
                165                 170                 175
Asp Glu Leu Ala Leu Ser Thr Leu Pro Pro Ala Ala Pro Ala Ser Gly
            180                 185                 190
Gln Ala Pro Ala Cys
        195

      <210> 17
      <211> 3102
      <212> DNA
      <213> H. sapiens

      <220>
      <221> CDS
      <222> (274)...(1705)
      <223> K+Hnov11

      <400> 17
gcacgcgcaa agcgcccacc gagacccctg gggtggagct tgtgttaata gaaacatacc      60
caccccccagc ctttcctggg aggggatcag acccctcaaa ctcttgcccc agcccagccc    120
ttcagcaccc aagacccacc aggaggcctg ggcccgccag taatgggtag ggagaggggg     180
ccccgccagg gcgcacggcg ctctcgccga cgctgttccc tccgcttcca ggtgtagcgc     240
ccccgcgcgg cgcgggcggc cggcgcctcc agc atg acc ggc cag agc ctg tgg     294
                                     Met Thr Gly Gln Ser Leu Trp
                                      1               5

gac gtg tcg gag gct aac gtc gag gac ggg gag atc cgc atc aat gtg      342
Asp Val Ser Glu Ala Asn Val Glu Asp Gly Glu Ile Arg Ile Asn Val
        10                  15                  20

ggc ggc ttc aag agg agg ctg cgc tcg cac acg ctg ctg cgc ttc ccc      390
Gly Gly Phe Lys Arg Arg Leu Arg Ser His Thr Leu Leu Arg Phe Pro
    25                  30                  35

gag acg cgc ctg ggc cgc ttg ctg ctc tgc cac tcg cgc gag gcc att      438
Glu Thr Arg Leu Gly Arg Leu Leu Leu Cys His Ser Arg Glu Ala Ile
40                  45                  50                  55

ctg gag ctc tgc gat gac tac gac gac gtc cag cgg gag ttc tac ttc      486
Leu Glu Leu Cys Asp Asp Tyr Asp Asp Val Gln Arg Glu Phe Tyr Phe
                60                  65                  70

gac cgc aac cct gag ctc ttc ccc tac gtg ctg cat ttc tat cac acc      534
Asp Arg Asn Pro Glu Leu Phe Pro Tyr Val Leu His Phe Tyr His Thr
            75                  80                  85
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ggc aag ctt cac gtc atg gct gag cta tgt gtc ttc tcc ttc agc cag 582
Gly Lys Leu His Val Met Ala Glu Leu Cys Val Phe Ser Phe Ser Gln
90 95 100

gag atc gag tac tgg ggc atc aac gag ttc ttc att gac tcc tgc tgc 630
Glu Ile Glu Tyr Trp Gly Ile Asn Glu Phe Phe Ile Asp Ser Cys Cys
105 110 115

agc tac agc tac cat ggc cgc aaa gta gag ccc gag cag gag aag tgg 678
Ser Tyr Ser Tyr His Gly Arg Lys Val Glu Pro Glu Gln Glu Lys Trp
120 125 130 135

gac gag cag agt gac cag gag agc acc acg tct tcc ttc gat gag atc 726
Asp Glu Gln Ser Asp Gln Glu Ser Thr Thr Ser Ser Phe Asp Glu Ile
140 145 150

ctt gcc ttc tac aac gac gcc tcc aag ttc gat ggg cag ccc ctc ggc 774
Leu Ala Phe Tyr Asn Asp Ala Ser Lys Phe Asp Gly Gln Pro Leu Gly
155 160 165

aac ttc cgc agg cag ctg tgg ctg gcg ctg gac aac ccc ggc tac tca 822
Asn Phe Arg Arg Gln Leu Trp Leu Ala Leu Asp Asn Pro Gly Tyr Ser
170 175 180

gtg ctg agc agg gtc ttc agc atc ctg tcc atc ctg gtg gtg atg ggg 870
Val Leu Ser Arg Val Phe Ser Ile Leu Ser Ile Leu Val Val Met Gly
185 190 195

tcc atc atc acc atg tgc ctc aat agc ctg ccc gat ttc caa atc cct 918
Ser Ile Ile Thr Met Cys Leu Asn Ser Leu Pro Asp Phe Gln Ile Pro
200 205 210 215

gac agc cag ggc aac cct ggc gag gac cct agg ttc gaa atc gtg gag 966
Asp Ser Gln Gly Asn Pro Gly Glu Asp Pro Arg Phe Glu Ile Val Glu
220 225 230

cac ttt ggc att gcc tgg ttc aca ttt gag ctg gtg gcc agg ttt gct 1014
His Phe Gly Ile Ala Trp Phe Thr Phe Glu Leu Val Ala Arg Phe Ala
235 240 245

gtg gcc cct gac ttc ctc aag ttc ttc aag aat gcc cta aac ctt att 1062
Val Ala Pro Asp Phe Leu Lys Phe Phe Lys Asn Ala Leu Asn Leu Ile
250 255 260

gac ctc atg tcc atc gtc ccc ttt tac atc act ctg gtg gtg aac ctg 1110
Asp Leu Met Ser Ile Val Pro Phe Tyr Ile Thr Leu Val Val Asn Leu
265 270 275

gtg gtg gag agc aca cct act tta gcc aac ttg ggc agg gtg gcc cag 1158
Val Val Glu Ser Thr Pro Thr Leu Ala Asn Leu Gly Arg Val Ala Gln
280 285 290 295

gtc ctg agg ctg atg cgg atc ttc cgc atc tta aag ctg gcc agg cac 1206
Val Leu Arg Leu Met Arg Ile Phe Arg Ile Leu Lys Leu Ala Arg His
300 305 310

tcc act ggc ctc cgc tcc ctg ggg gcc act ttg aaa tac agc tac aaa 1254
Ser Thr Gly Leu Arg Ser Leu Gly Ala Thr Leu Lys Tyr Ser Tyr Lys
315 320 325

gaa gta ggg ctg ctc ttg ctc tac ctc tcc gtg ggg att tcc atc ttc 1302

```
Glu Val Gly Leu Leu Leu Leu Tyr Leu Ser Val Gly Ile Ser Ile Phe
        330                 335                 340

tcc gtg gtg gcc tac acc att gaa aag gag gag aac gag ggc ctg gcc      1350
Ser Val Val Ala Tyr Thr Ile Glu Lys Glu Glu Asn Glu Gly Leu Ala
    345                 350                 355

acc atc cct gcc tgc tgg tgg tgg gct acc gtc agt atg acc aca gtg      1398
Thr Ile Pro Ala Cys Trp Trp Trp Ala Thr Val Ser Met Thr Thr Val
360                 365                 370                 375

ggg tac ggg gat gtg gtc cca ggg acc acg gca gga aag ctg act gcc      1446
Gly Tyr Gly Asp Val Val Pro Gly Thr Thr Ala Gly Lys Leu Thr Ala
                380                 385                 390

tct gcc tgc atc ttg gca ggc atc ctc gtg gtg gtc ctg ccc atc acc      1494
Ser Ala Cys Ile Leu Ala Gly Ile Leu Val Val Val Leu Pro Ile Thr
            395                 400                 405

ttg atc ttc aat aag ttc tcc cac ttt tac cgg cgc caa aag caa ctt      1542
Leu Ile Phe Asn Lys Phe Ser His Phe Tyr Arg Arg Gln Lys Gln Leu
        410                 415                 420

gag agt gcc atg cgc agc tgt gac ttt gga gat gga atg aag gag gtc      1590
Glu Ser Ala Met Arg Ser Cys Asp Phe Gly Asp Gly Met Lys Glu Val
    425                 430                 435

cct tcg gtc aat tta agg gac tat tat gcc cat aaa gtt aaa tcc ctt      1638
Pro Ser Val Asn Leu Arg Asp Tyr Tyr Ala His Lys Val Lys Ser Leu
440                 445                 450                 455

atg gca agc ctg acg aac atg agc agg agc tca cca agt gaa ctc agt      1686
Met Ala Ser Leu Thr Asn Met Ser Arg Ser Ser Pro Ser Glu Leu Ser
                460                 465                 470

tta aat gat tcc cta cgt t agccgggagg acttgtcacc ctccacccca           1735
Leu Asn Asp Ser Leu Arg
            475

cattgctgag ctgcctcttg tgcctctggc acagcccagg caccttatgg ttatggtgta   1795
aggagtatgc ccagcccctg aggggagaga tgcatgggat atgcacccag gtttctttta   1855
cagtttttag aatcgttttt agagggtggt gtgtctgaca ccatgccttt gcacctttcc   1915
atgaaatgac actcactggt ctttgcatcg tgggcataaa atgttcacct tttttccaga   1975
tgagtacacc cagaatgcta atttttctgt ccatcgtgta cgctattcta gtgcttgtgg   2035
cccagtactg tctatgagtt gtcgtgctcc tgtttctgag gttgtcgtgt gagttctgta   2095
caaaaagccc ccacaagtcg tccagtagaa atgcatctat gaggtcagca aggatatgat   2155
gagattttgc tcacagtcat gtgaaaacaa aatctcagct ctttatccat tgctttcact   2215
tagttttagt accaaaacaa agagaatgca aagttaagca gacttgacca atgcaagtct   2275
ctaagttgtt tttataaatg atctgtagtt ccgtggcttg catgggtgca ccaatcatct   2335
ttagaacgat gtacactgat gttcatctca taaatgtcac tctttagaga atgttactta   2395
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Glu Leu Val Ala Arg Phe Ala Val Ala Pro Asp Phe Leu Lys Phe Phe
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Lys Asn Ala Leu Asn Leu Ile Asp Leu Met Ser Ile Val Pro Phe Tyr
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Thr Ala Gly Lys Leu Thr Ala Ser Ala Cys Ile Leu Ala Gly Ile Leu
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Val Val Val Leu Pro Ile Thr Leu Ile Phe Asn Lys Phe Ser His Phe
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Gly Asp Gly Met Lys Glu Val Pro Ser Val Asn Leu Arg Asp Tyr Tyr
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Gly Cys Ala Cys Ser Phe Leu Tyr Gly Pro Asp Thr Ser Glu Leu Val
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80 85 90

gag ctg atc ctg tac cgg aag agc ggg ctc ccg ttc tgg tgt ctc ctg 578
Glu Leu Ile Leu Tyr Arg Lys Ser Gly Leu Pro Phe Trp Cys Leu Leu
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Asp Val Ile Pro Ile Lys Asn Glu Lys Gly Glu Val Ala Leu Phe Leu
115 120 125

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Val Ser His Lys Asp Ile Ser Glu Thr Lys Asn Arg Gly Gly Pro Asp
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Ser Lys Gly Phe Asn Ala Asn Arg Arg Arg Ser Arg Ala Val Leu Tyr
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cac ctg tcc ggg cac ctg cag aag cag ccc aag ggc aag cac aag ctc 818
His Leu Ser Gly His Leu Gln Lys Gln Pro Lys Gly Lys His Lys Leu
175 180 185 190

aat aag ggg gtg ttt ggg gag aaa cca aac ttg cct gag tac aaa gta 866
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gtc act gtg ccc tac agc gtg tgt gtg agc aca gca cgg gag ccc agt 1010
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gcc gcc cgc ggc ccg ccc agc gtc tgt gac ctg gcc gtg gag gtc ctc 1058
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Phe Ile Leu Asp Ile Val Leu Asn Phe Arg Thr Thr Phe Val Ser Lys
275 280 285

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Ser Gly Gln Val Val Phe Ala Pro Lys Ser Ile Cys Leu His Tyr Val
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acc acc tgg ttc ctg ctg gat gtc atc gca gcg ctg ccc ttt gac ctg 1202
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320 325 330

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335 340 345 350

tac tcg cag tac agc gcc gtg gtg ctg aca ctg ctc atg gcc gtg ttc 1346
Tyr Ser Gln Tyr Ser Ala Val Val Leu Thr Leu Leu Met Ala Val Phe
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Ala Leu Leu Ala His Trp Val Ala Cys Val Trp Phe Tyr Ile Gly Gln
370 375 380

cgg gag atc gag agc agc gaa tcc gag ctg cct gag att ggc tgg ctg 1442
Arg Glu Ile Glu Ser Ser Glu Ser Glu Leu Pro Glu Ile Gly Trp Leu
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cag gag ctg gcc cgc cga ctg gag act ccc tac tac ctg gtg ggc cgg 1490
Gln Glu Leu Ala Arg Arg Leu Glu Thr Pro Tyr Tyr Leu Val Gly Arg
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Arg Pro Ala Gly Gly Asn Ser Ser Gly Gln Ser Asp Asn Cys Ser Ser
415 420 425 430

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Ser Ser Glu Ala Asn Gly Thr Gly Leu Glu Leu Leu Gly Gly Pro Ser
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acc agc gtg ggc ttc ggc aac gtg tcc gcc aac acg gac acc gag aag 1682
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Ile Phe Ser Ile Cys Thr Met Leu Ile Gly Ala Leu Met His Ala Val
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Val Phe Gly Asn Val Thr Ala Ile Ile Gln Arg Met Tyr Ala Arg Arg
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Phe Leu Tyr His Ser Arg Thr Arg Asp Gln Arg Asp Tyr Ile Arg Ile
515 520 525

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Tyr Leu Ile His Gln Gly Asp Ala Leu Gln Ala Leu Tyr Phe Val Cys
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tct ggc tcc atg gag gtg ctc aag ggt ggc acc gtg ctc gcc atc cta 2162
Ser Gly Ser Met Glu Val Leu Lys Gly Gly Thr Val Leu Ala Ile Leu
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Cys Leu Gln Leu Ala Gly Leu His Asp Ser Leu Ala Leu Tyr Pro Glu
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Gly Asp Asn Thr Leu Met Ser Thr Leu Glu Glu Lys Glu Thr Asp Gly
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Pro Leu Leu Ser Pro Gly Cys Thr Ser Ser Ser Ser Ala Ala Lys Leu
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Leu Ser Pro Arg Arg Thr Ala Pro Arg Pro Arg Leu Gly Gly Arg Gly
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agg cca ggc agg gca ggg gct ttg aag gct gag gct ggc ccc tct gct      2642
Arg Pro Gly Arg Ala Gly Ala Leu Lys Ala Glu Ala Gly Pro Ser Ala
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ccc cca cgg gcc cta gag ggg cta cgg ctg ccc ccc atg cca tgg aat      2690
Pro Pro Arg Ala Leu Glu Gly Leu Arg Leu Pro Pro Met Pro Trp Asn
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Val Pro Pro Asp Leu Ser Pro Arg Val Val Asp Gly Ile Glu Asp Gly
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Cys Gly Ser Asp Gln Pro Lys Phe Ser Phe Arg Val Gly Gln Ser Gly
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ccg gaa tgt agc agc agc ccc tcc cct gga cca gag agc ggc ctg ctc      2834
Pro Glu Cys Ser Ser Ser Pro Ser Pro Gly Pro Glu Ser Gly Leu Leu
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act gtt ccc cat ggg ccc agc gag gca agg aac aca gac aca ctg gac      2882
Thr Val Pro His Gly Pro Ser Glu Ala Arg Asn Thr Asp Thr Leu Asp
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aag ctt cgg cag gcg gtg aca gag ctg tca gag cag gtg ctg cag atg      2930
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Arg Glu Gly Leu Gln Ser Leu Arg Gln Ala Val Gln Leu Val Leu Ala
895 900 905 910

ccc cac agg gag ggt ccg tgc cct cgg gca tcg gga gag ggg ccg tgc 3026
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cca gcc agc acc tcc ggg ctt ctg cag cct ctg tgt gtg gac act ggg 3074
Pro Ala Ser Thr Ser Gly Leu Leu Gln Pro Leu Cys Val Asp Thr Gly
930 935 940

gca tcc tcc tac tgc ctg cag ccc cca gct ggc tct gtc ttg agt ggg 3122
Ala Ser Ser Tyr Cys Leu Gln Pro Pro Ala Gly Ser Val Leu Ser Gly
945 950 955

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Thr Trp Pro His Pro Arg Pro Gly Pro Pro Pro Leu Met Ala Pro Arg
960 965 970

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Pro Trp Gly Pro Pro Ala Ser Gln Ser Ser Pro Trp Pro Arg Ala Thr
975 980 985 990

gct ttc tgg acc tcc acc tca gac tca gag ccc cct gcc tca gga gac 3266
Ala Phe Trp Thr Ser Thr Ser Asp Ser Glu Pro Pro Ala Ser Gly Asp
995 1000 1005

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Ala Cys Ser Phe Leu Tyr Gly Pro Asp Thr Ser Glu Leu Val Arg Gln
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Gln Ile Arg Lys Ala Leu Asp Glu His Lys Glu Phe Lys Ala Glu Leu
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Ile Leu Tyr Arg Lys Ser Gly Leu Pro Phe Trp Cys Leu Leu Asp Val
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Ser Gly His Leu Gln Lys Gln Pro Lys Gly Lys His Lys Leu Asn Lys
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Ala Gly Gly Asn Ser Ser Gly Gln Ser Asp Asn Cys Ser Ser Ser Ser
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Glu Ala Asn Gly Thr Gly Leu Glu Leu Leu Gly Gly Pro Ser Leu Arg
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Ser Ala Tyr Ile Thr Ser Leu Tyr Phe Ala Leu Ser Ser Leu Thr Ser
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Pro Asp Glu Leu Arg Ala Asp Ile Ala Met His Leu His Lys Glu Val
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Gln Leu Ala Gly Leu His Asp Ser Leu Ala Leu Tyr Pro Glu Phe Ala
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755 760 765
Pro Arg Arg Thr Ala Pro Arg Pro Arg Leu Gly Gly Arg Gly Arg Pro
770 775 780
Gly Arg Ala Gly Ala Leu Lys Ala Glu Ala Gly Pro Ser Ala Pro Pro
785 790 795 800
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Ser Tyr Cys Leu Gln Pro Pro Ala Gly Ser Val Leu Ser Gly Thr Trp

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Ser Glu Pro Ser Thr Pro Ala Ser Pro Pro Pro Ser Glu Glu Gly Ala
    1010                1015                1020
Arg Thr Gly Pro Ala Glu Pro Val Ser Gln Ala Glu Ala Thr Ser Thr
1025                1030                1035                104
Gly Glu Pro Pro Pro Gly Ser Gly Gly Leu Ala Leu Pro Trp Asp Pro
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acatgtagaa ggccctaggg gaatgctttc ttccccagat ctttgccctg tagtaggttt   180
cagctgagca aggacgagta gtttttctgg tgtttggcct cctctgttgg gtggaaaaag   240
actttcttct ctattttcct agttatatat gctatcatat gtctgttttt ctcctcttga   300
agtttccctg aaacctgggc tcttgaagac gcatcactgg agcag atg gat aat gga   357
                                                  Met Asp Asn Gly
                                                   1

gac tgg ggc tat atg atg act gac cca gtc aca tta aat gta ggt gga     405
Asp Trp Gly Tyr Met Met Thr Asp Pro Val Thr Leu Asn Val Gly Gly
 5                  10                  15                  20

cac ttg tat aca acg tct ctc acc aca ttg acg cgt tac ccg gat tcc     453
His Leu Tyr Thr Thr Ser Leu Thr Thr Leu Thr Arg Tyr Pro Asp Ser
                25                  30                  35

atg ctt gga gct atg ttt ggg ggg gac ttc ccc aca gct cga gac cct     501
Met Leu Gly Ala Met Phe Gly Gly Asp Phe Pro Thr Ala Arg Asp Pro
            40                  45                  50

caa ggc aat tac ttt att gat cga gat gga cct ctt ttc cga tat gtc     549
Gln Gly Asn Tyr Phe Ile Asp Arg Asp Gly Pro Leu Phe Arg Tyr Val
        55                  60                  65

ctc aac ttc tta aga act tca gaa ttg acc tta ccg ttg gat ttt aag     597
Leu Asn Phe Leu Arg Thr Ser Glu Leu Thr Leu Pro Leu Asp Phe Lys
    70                  75                  80

gaa ttt gat ctg ctt cgg aaa gaa gca gat ttt tac cag att gag ccc     645
Glu Phe Asp Leu Leu Arg Lys Glu Ala Asp Phe Tyr Gln Ile Glu Pro
 85                 90                  95                  100
```

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ttg att cag tgt ctc aat gat cct aag cct ttg tat ccc atg gat act      693
Leu Ile Gln Cys Leu Asn Asp Pro Lys Pro Leu Tyr Pro Met Asp Thr
                105                 110                 115

ttt gaa gaa gtt gtg gag ctg tct agt act cgg aag ctt tct aag tac      741
Phe Glu Glu Val Val Glu Leu Ser Ser Thr Arg Lys Leu Ser Lys Tyr
            120                 125                 130

tcc aac cca gtg gct gtc atc ata acg caa cta acc atc acc act aag      789
Ser Asn Pro Val Ala Val Ile Ile Thr Gln Leu Thr Ile Thr Thr Lys
        135                 140                 145

gtc cat tcc tta cta gaa ggc atc tca aat tat ttt acc aag tgg aat      837
Val His Ser Leu Leu Glu Gly Ile Ser Asn Tyr Phe Thr Lys Trp Asn
    150                 155                 160

aag cac atg atg gac acc aga gac tgc cag gtt tcc ttt act ttt gga      885
Lys His Met Met Asp Thr Arg Asp Cys Gln Val Ser Phe Thr Phe Gly
165                 170                 175                 180

ccc tgt gat tat cac cag gaa gtt tct ctt agg gtc cac ctg atg gaa      933
Pro Cys Asp Tyr His Gln Glu Val Ser Leu Arg Val His Leu Met Glu
                185                 190                 195

tac att aca aaa caa ggt ttc acg atc cgc aac acc cgg gtg cat cac      981
Tyr Ile Thr Lys Gln Gly Phe Thr Ile Arg Asn Thr Arg Val His His
            200                 205                 210

atg agt gag cgg gcc aat gaa aac aca gtg gag cac aac tgg act ttc     1029
Met Ser Glu Arg Ala Asn Glu Asn Thr Val Glu His Asn Trp Thr Phe
        215                 220                 225

tgt agg cta gcc cgg aag aca gac gac t gatctccgac cctgccacag         1077
Cys Arg Leu Ala Arg Lys Thr Asp Asp
    230                 235

gttcctggaa agactctcca ggaaatggaa gatactgatt tttttttta aatcacagtg    1137
tgagatattt tttttctttt aaatagttgt atttatttga aggcagtgag gaccagaagg   1197
aagttttgtg ctttggcaga ctcctccatg ttttgttccc ttcccccctga gtatgcatgt  1257
gcctgttcag agtctccaga taccttttttt ataaaaagaa gtctgaaaat cattatggta  1317
tataatctac ccttaacaga gcttttctta ttacagtgct aaaatgattt ctgataaaat   1377
ggtccctaac tcaactagaa ggctaaaaat acaagaatga aagaataagc agagtactca   1437
tgatgccttt gagaaaaatc aaaacatcat gtagggtgac ctagtttcca aaccaataaa   1497
taagtagtat tgtaatatta aaggaaaact gttccaatca tttaaaagta cttattaagt   1557
actgcttttt acagttatga caactgtttc tttctatgca tataaatcaa ggaaccaaat   1617
atctgtagcc atggaaatgt ctgactagaa atatttatat tgaattctga atacaaaatg   1677
tccctgtggt agaaaactta ctctttatgc ctggtgcagt ataattccca agtgtactgt   1737
ctaccagaaa aaaaaaacaa aactaataaa aaatgaaata tgaaaaaaaa aaaaaaaaaa   1797
aaa                                                                 1800
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<210> 22
<211> 1836
<212> DNA
<213> H. sapiens

<220>
<221> CDS
<222> (382)...(1093)
<223> K+Hnov28 splice 2

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acctatagct tctctcttct agaccacatg gttgggaaag gagaaagaga aaatgattac     120
ttgtagagaa aaatccattt ctgcagtggt atggttaagg ataatctaac cataatcaca     180
ttatccttgt atgcctggct acttgtgctg gcctgtatgt gaatgttaac cccaaagact     240
cctttagatg tcgctgaact agttactata aaaagtattt cgctttcaaa ctcccacatt     300
tcaagaagag caaaactcaa tacaaggcaa ttttgaagtt tccctgaaac ctgggctctt     360
gaagacgcat cactggagca g atg gat aat gga gac tgg ggc tat atg atg       411
                        Met Asp Asn Gly Asp Trp Gly Tyr Met Met
                        1               5                   10

act gac cca gtc aca tta aat gta ggt gga cac ttg tat aca acg tct       459
Thr Asp Pro Val Thr Leu Asn Val Gly Gly His Leu Tyr Thr Thr Ser
                15                  20                  25

ctc acc aca ttg acg cgt tac ccg gat tcc atg ctt gga gct atg ttt       507
Leu Thr Thr Leu Thr Arg Tyr Pro Asp Ser Met Leu Gly Ala Met Phe
            30                  35                  40

ggg ggg gac ttc ccc aca gct cga gac cct caa ggc aat tac ttt att       555
Gly Gly Asp Phe Pro Thr Ala Arg Asp Pro Gln Gly Asn Tyr Phe Ile
        45                  50                  55

gat cga gat gga cct ctt ttc cga tat gtc ctc aac ttc tta aga act       603
Asp Arg Asp Gly Pro Leu Phe Arg Tyr Val Leu Asn Phe Leu Arg Thr
    60                  65                  70

tca gaa ttg acc tta ccg ttg gat ttt aag gaa ttt gat ctg ctt cgg       651
Ser Glu Leu Thr Leu Pro Leu Asp Phe Lys Glu Phe Asp Leu Leu Arg
75                  80                  85                  90

aaa gaa gca gat ttt tac cag att gag ccc ttg att cag tgt ctc aat       699
Lys Glu Ala Asp Phe Tyr Gln Ile Glu Pro Leu Ile Gln Cys Leu Asn
                95                  100                 105

gat cct aag cct ttg tat ccc atg gat act ttt gaa gaa gtt gtg gag       747
Asp Pro Lys Pro Leu Tyr Pro Met Asp Thr Phe Glu Glu Val Val Glu
            110                 115                 120

ctg tct agt act cgg aag ctt tct aag tac tcc aac cca gtg gct gtc       795
Leu Ser Ser Thr Arg Lys Leu Ser Lys Tyr Ser Asn Pro Val Ala Val
        125                 130                 135

atc ata acg caa cta acc atc acc act aag gtc cat tcc tta cta gaa       843
Ile Ile Thr Gln Leu Thr Ile Thr Thr Lys Val His Ser Leu Leu Glu
    140                 145                 150

ggc atc tca aat tat ttt acc aag tgg aat aag cac atg atg gac acc       891
Gly Ile Ser Asn Tyr Phe Thr Lys Trp Asn Lys His Met Met Asp Thr
155                 160                 165                 170

aga gac tgc cag gtt tcc ttt act ttt gga ccc tgt gat tat cac cag       939
Arg Asp Cys Gln Val Ser Phe Thr Phe Gly Pro Cys Asp Tyr His Gln
                175                 180                 185

gaa gtt tct ctt agg gtc cac ctg atg gaa tac att aca aaa caa ggt       987
Glu Val Ser Leu Arg Val His Leu Met Glu Tyr Ile Thr Lys Gln Gly
            190                 195                 200

ttc acg atc cgc aac acc cgg gtg cat cac atg agt gag cgg gcc aat      1035
Phe Thr Ile Arg Asn Thr Arg Val His His Met Ser Glu Arg Ala Asn
```

205 210 215

gaa aac aca gtg gag cac aac tgg act ttc tgt agg cta gcc cgg aag 1083
Glu Asn Thr Val Glu His Asn Trp Thr Phe Cys Arg Leu Ala Arg Lys
220 225 230

aca gac gac t gatctccgac cctgccacag gttcctggaa agactctcca 1133
Thr Asp Asp
235

ggaaatggaa gatactgatt ttttttttta aatcacagtg tgagatattt tttttctttt 1193
aaatagttgt atttatttga aggcagtgag gaccagaagg aagttttgtg ctttggcaga 1253
ctcctccatg ttttgttccc ttccccctga gtatgcatgt gcctgttcag agtctccaga 1313
tacctttttt ataaaaagaa gtctgaaaat cattatggta tataatctac ccttaacaga 1373
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ggctaaaaat acaagaatga aagaataagc agagtactca tgatgccttt gagaaaaatc 1493
aaaacatcat gtagggtgac ctagtttcca aaccaataaa taagtagtat tgtaatatta 1553
aaggaaaact gttccaatca tttaaaagta cttattaagt actgcttttt acagttatga 1613
caactgtttc tttctatgca tataaatcaa ggaaccaaat atctgtagcc atggaaatgt 1673
ctgactagaa atatttatat tgaattctga atacaaaatg tccctgtggt agaaaactta 1733
ctctttatgc ctggtgcagt ataattccca agtgtactgt ctaccagaaa aaaaaaacaa 1793
aactaataaa aaatgaaata tgaaaaaaaa aaaaaaaaaa aaa 1836

<210> 23
<211> 1751
<212> DNA
<213> H. sapiens

<220>
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<222> (297)...(1008)
<223> K+Hnov28 splice 3

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ggttgatttg ggattgaagt gtgtgagagg gaactgacta aggcagttca gtagctggga 120
aactgtttgt ttaaatgctt ttgaattgta gataaaaata aattcacatt ggcatcatta 180
gtatctgagc atttctcagt gtcttaaggc tggctctcca tgagtgctgg ctgattgact 240
ctcatctata tcgtttccct gaaacctggg ctcttgaaga cgcatcactg gagcag atg 299
Met
1

gat aat gga gac tgg ggc tat atg atg act gac cca gtc aca tta aat 347
Asp Asn Gly Asp Trp Gly Tyr Met Met Thr Asp Pro Val Thr Leu Asn
5 10 15

gta ggt gga cac ttg tat aca acg tct ctc acc aca ttg acg cgt tac 395
Val Gly Gly His Leu Tyr Thr Thr Ser Leu Thr Thr Leu Thr Arg Tyr
20 25 30

ccg gat tcc atg ctt gga gct atg ttt ggg ggg gac ttc ccc aca gct 443
Pro Asp Ser Met Leu Gly Ala Met Phe Gly Gly Asp Phe Pro Thr Ala
35 40 45

cga gac cct caa ggc aat tac ttt att gat cga gat gga cct ctt ttc 491
Arg Asp Pro Gln Gly Asn Tyr Phe Ile Asp Arg Asp Gly Pro Leu Phe
50 55 60 65

cga tat gtc ctc aac ttc tta aga act tca gaa ttg acc tta ccg ttg 539
Arg Tyr Val Leu Asn Phe Leu Arg Thr Ser Glu Leu Thr Leu Pro Leu
70 75 80

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gat ttt aag gaa ttt gat ctg ctt cgg aaa gaa gca gat ttt tac cag      587
Asp Phe Lys Glu Phe Asp Leu Leu Arg Lys Glu Ala Asp Phe Tyr Gln
                 85                  90                  95

att gag ccc ttg att cag tgt ctc aat gat cct aag cct ttg tat ccc      635
Ile Glu Pro Leu Ile Gln Cys Leu Asn Asp Pro Lys Pro Leu Tyr Pro
        100                 105                 110

atg gat act ttt gaa gaa gtt gtg gag ctg tct agt act cgg aag ctt      683
Met Asp Thr Phe Glu Glu Val Val Glu Leu Ser Ser Thr Arg Lys Leu
    115                 120                 125

tct aag tac tcc aac cca gtg gct gtc atc ata acg caa cta acc atc      731
Ser Lys Tyr Ser Asn Pro Val Ala Val Ile Ile Thr Gln Leu Thr Ile
130                 135                 140                 145

acc act aag gtc cat tcc tta cta gaa ggc atc tca aat tat ttt acc      779
Thr Thr Lys Val His Ser Leu Leu Glu Gly Ile Ser Asn Tyr Phe Thr
                150                 155                 160

aag tgg aat aag cac atg atg gac acc aga gac tgc cag gtt tcc ttt      827
Lys Trp Asn Lys His Met Met Asp Thr Arg Asp Cys Gln Val Ser Phe
            165                 170                 175

act ttt gga ccc tgt gat tat cac cag gaa gtt tct ctt agg gtc cac      875
Thr Phe Gly Pro Cys Asp Tyr His Gln Glu Val Ser Leu Arg Val His
        180                 185                 190

ctg atg gaa tac att aca aaa caa ggt ttc acg atc cgc aac acc cgg      923
Leu Met Glu Tyr Ile Thr Lys Gln Gly Phe Thr Ile Arg Asn Thr Arg
    195                 200                 205

gtg cat cac atg agt gag cgg gcc aat gaa aac aca gtg gag cac aac      971
Val His His Met Ser Glu Arg Ala Asn Glu Asn Thr Val Glu His Asn
210                 215                 220                 225

tgg act ttc tgt agg cta gcc cgg aag aca gac gac t gatctccgac        1018
Trp Thr Phe Cys Arg Leu Ala Arg Lys Thr Asp Asp
                230                 235

cctgccacag gttcctggaa agactctcca ggaaatggaa gatactgatt ttttttttta   1078
aatcacagtg tgagatattt tttttctttt aaatagttgt atttatttga aggcagtgag   1138
gaccagaagg aagtttttgtg ctttggcaga ctcctccatg ttttgttccc ttccccctga  1198
gtatgcatgt gcctgttcag agtctccaga taccttttttt ataaaaagaa gtctgaaaat  1258
cattatggta tataatctac ccttaacaga gcttttctta ttacagtgct aaaatgattt   1318
ctgataaaat ggtccctaac tcaactagaa ggctaaaaat acaagaatga aagaataagc   1378
agagtactca tgatgccttt gagaaaaatc aaaacatcat gtagggtgac ctagtttcca   1438
aaccaataaa taagtagtat tgtaatatta aaggaaaact gttccaatca tttaaaagta   1498
cttattaagt actgcttttt acagttatga caactgtttc tttctatgca tataaatcaa   1558
ggaaccaaat atctgtagcc atggaaatgt ctgactagaa atatttatat tgaattctga   1618
atacaaaatg tccctgtggt agaaaactta ctctttatgc ctggtgcagt ataattccca   1678
agtgtactgt ctaccagaaa aaaaaaacaa aactaataaa aaatgaaata tgaaaaaaaa   1738
aaaaaaaaaa aaa                                                      1751
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<210> 24
<211> 1542
<212> DNA
<213> H. sapiens

<220>

<221> CDS
<222> (88)...(799)
<223> K+Hnov28, splice 4

<400> 24

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gctcttgaag acgcatcact ggagcag atg gat aat gga gac tgg ggc tat atg    114
                              Met Asp Asn Gly Asp Trp Gly Tyr Met
                               1               5

atg act gac cca gtc aca tta aat gta ggt gga cac ttg tat aca acg      162
Met Thr Asp Pro Val Thr Leu Asn Val Gly Gly His Leu Tyr Thr Thr
 10                  15                  20                  25

tct ctc acc aca ttg acg cgt tac ccg gat tcc atg ctt gga gct atg      210
Ser Leu Thr Thr Leu Thr Arg Tyr Pro Asp Ser Met Leu Gly Ala Met
                 30                  35                  40

ttt ggg ggg gac ttc ccc aca gct cga gac cct caa ggc aat tac ttt      258
Phe Gly Gly Asp Phe Pro Thr Ala Arg Asp Pro Gln Gly Asn Tyr Phe
             45                  50                  55

att gat cga gat gga cct ctt ttc cga tat gtc ctc aac ttc tta aga      306
Ile Asp Arg Asp Gly Pro Leu Phe Arg Tyr Val Leu Asn Phe Leu Arg
         60                  65                  70

act tca gaa ttg acc tta ccg ttg gat ttt aag gaa ttt gat ctg ctt      354
Thr Ser Glu Leu Thr Leu Pro Leu Asp Phe Lys Glu Phe Asp Leu Leu
     75                  80                  85

cgg aaa gaa gca gat ttt tac cag att gag ccc ttg att cag tgt ctc      402
Arg Lys Glu Ala Asp Phe Tyr Gln Ile Glu Pro Leu Ile Gln Cys Leu
 90                  95                 100                 105

aat gat cct aag cct ttg tat ccc atg gat act ttt gaa gaa gtt gtg      450
Asn Asp Pro Lys Pro Leu Tyr Pro Met Asp Thr Phe Glu Glu Val Val
                110                 115                 120

gag ctg tct agt act cgg aag ctt tct aag tac tcc aac cca gtg gct      498
Glu Leu Ser Ser Thr Arg Lys Leu Ser Lys Tyr Ser Asn Pro Val Ala
            125                 130                 135

gtc atc ata acg caa cta acc atc acc act aag gtc cat tcc tta cta      546
Val Ile Ile Thr Gln Leu Thr Ile Thr Thr Lys Val His Ser Leu Leu
        140                 145                 150

gaa ggc atc tca aat tat ttt acc aag tgg aat aag cac atg atg gac      594
Glu Gly Ile Ser Asn Tyr Phe Thr Lys Trp Asn Lys His Met Met Asp
    155                 160                 165

acc aga gac tgc cag gtt tcc ttt act ttt gga ccc tgt gat tat cac      642
Thr Arg Asp Cys Gln Val Ser Phe Thr Phe Gly Pro Cys Asp Tyr His
170                 175                 180                 185

cag gaa gtt tct ctt agg gtc cac ctg atg gaa tac att aca aaa caa      690
Gln Glu Val Ser Leu Arg Val His Leu Met Glu Tyr Ile Thr Lys Gln
                190                 195                 200

ggt ttc acg atc cgc aac acc cgg gtg cat cac atg agt gag cgg gcc      738
Gly Phe Thr Ile Arg Asn Thr Arg Val His His Met Ser Glu Arg Ala
            205                 210                 215
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aat gaa aac aca gtg gag cac aac tgg act ttc tgt agg cta gcc cgg      786
Asn Glu Asn Thr Val Glu His Asn Trp Thr Phe Cys Arg Leu Ala Arg
        220                 225                 230

aag aca gac gac t gatctccgac cctgccacag gttcctggaa agactctcca        839
Lys Thr Asp Asp
    235

ggaaatggaa gatactgatt ttttttttta aatcacagtg tgagatattt tttttctttt    899
aaatagttgt atttatttga aggcagtgag gaccagaagg aagttttgtg ctttggcaga    959
ctcctccatg ttttgttccc ttccccctga gtatgcatgt gcctgttcag agtctccaga   1019
tacctttttt ataaaaagaa gtctgaaaat cattatggta tataatctac ccttaacaga   1079
gcttttctta ttacagtgct aaaatgattt ctgataaaat ggtccctaac tcaactagaa   1139
ggctaaaaat acaagaatga aagaataagc agagtactca tgatgccttt gagaaaaatc   1199
aaaacatcat gtagggtgac ctagtttcca aaccaataaa taagtagtat tgtaatatta   1259
aaggaaaact gttccaatca tttaaaagta cttattaagt actgcttttt acagttatga   1319
caactgtttc tttctatgca tataaatcaa ggaaccaaat atctgtagcc atggaaatgt   1379
ctgactagaa atatttatat tgaattctga atacaaaatg tccctgtggt agaaaactta   1439
ctctttatgc ctggtgcagt ataattccca agtgtactgt ctaccagaaa aaaaaaacaa   1499
aactaataaa aaatgaaata tgaaaaaaaa aaaaaaaaaa aaa                     1542

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      <211> 237
      <212> PRT
      <213> H. sapiens

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Met Asp Asn Gly Asp Trp Gly Tyr Met Met Thr Asp Pro Val Thr Leu
 1               5                  10                  15
Asn Val Gly Gly His Leu Tyr Thr Thr Ser Leu Thr Thr Leu Thr Arg
            20                  25                  30
Tyr Pro Asp Ser Met Leu Gly Ala Met Phe Gly Gly Asp Phe Pro Thr
        35                  40                  45
Ala Arg Asp Pro Gln Gly Asn Tyr Phe Ile Asp Arg Asp Gly Pro Leu
    50                  55                  60
Phe Arg Tyr Val Leu Asn Phe Leu Arg Thr Ser Glu Leu Thr Leu Pro
65                  70                  75                  80
Leu Asp Phe Lys Glu Phe Asp Leu Leu Arg Lys Glu Ala Asp Phe Tyr
                85                  90                  95
Gln Ile Glu Pro Leu Ile Gln Cys Leu Asn Asp Pro Lys Pro Leu Tyr
            100                 105                 110
Pro Met Asp Thr Phe Glu Glu Val Val Glu Leu Ser Ser Thr Arg Lys
        115                 120                 125
Leu Ser Lys Tyr Ser Asn Pro Val Ala Val Ile Ile Thr Gln Leu Thr
    130                 135                 140
Ile Thr Thr Lys Val His Ser Leu Leu Glu Gly Ile Ser Asn Tyr Phe
145                 150                 155                 160
Thr Lys Trp Asn Lys His Met Met Asp Thr Arg Asp Cys Gln Val Ser
                165                 170                 175
Phe Thr Phe Gly Pro Cys Asp Tyr His Gln Glu Val Ser Leu Arg Val
            180                 185                 190
His Leu Met Glu Tyr Ile Thr Lys Gln Gly Phe Thr Ile Arg Asn Thr
        195                 200                 205
Arg Val His His Met Ser Glu Arg Ala Asn Glu Asn Thr Val Glu His
    210                 215                 220
Asn Trp Thr Phe Cys Arg Leu Ala Arg Lys Thr Asp Asp
225                 230                 235

      <210> 26
      <211> 3204
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<212> DNA
<213> H. sapiens

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<222> (182)...(1349)
<223> K+Hnov42

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ggtggcgaag ggaggcgaat ccgagtgggt ggagggaggg gaagggcggg aggagaaaaa 120
ggtgggagga ggaccaggtg ggagggtggc ggctcactca ggacccagcg ggggcagcgc 180
g atg agg cgg gtg acc ctg ttc ctg aac ggc agc ccc aag aac gga aag 229
Met Arg Arg Val Thr Leu Phe Leu Asn Gly Ser Pro Lys Asn Gly Lys
1 5 10 15

gtg gtt gct gta tat gga act tta tct gat ttg ctt tct gtg gcc agc 277
Val Val Ala Val Tyr Gly Thr Leu Ser Asp Leu Leu Ser Val Ala Ser
20 25 30

agt aaa ctc ggc ata aaa gcc acc agt gtg tat aat ggg aaa ggt gga 325
Ser Lys Leu Gly Ile Lys Ala Thr Ser Val Tyr Asn Gly Lys Gly Gly
35 40 45

ctg att gat gat att gct ttg atc agg gat gat gat gtt ttg ttt gtt 373
Leu Ile Asp Asp Ile Ala Leu Ile Arg Asp Asp Asp Val Leu Phe Val
50 55 60

tgt gaa gga gag cca ttt att gat cct cag aca gat tct aag cct cct 421
Cys Glu Gly Glu Pro Phe Ile Asp Pro Gln Thr Asp Ser Lys Pro Pro
65 70 75 80

gag gga ttg tta gga ttc cac aca gac tgg ctg aca tta aat gtt gga 469
Glu Gly Leu Leu Gly Phe His Thr Asp Trp Leu Thr Leu Asn Val Gly
85 90 95

ggg cgg tac ttt aca act aca cgg agc act tta gtg aat aaa gaa cct 517
Gly Arg Tyr Phe Thr Thr Thr Arg Ser Thr Leu Val Asn Lys Glu Pro
100 105 110

gac agt atg ctg gcc cac atg ttt aag gac aaa ggt gtc tgg gga aat 565
Asp Ser Met Leu Ala His Met Phe Lys Asp Lys Gly Val Trp Gly Asn
115 120 125

aag caa gat cat aga gga gct ttc tta att gac cga agt cct gag tac 613
Lys Gln Asp His Arg Gly Ala Phe Leu Ile Asp Arg Ser Pro Glu Tyr
130 135 140

ttc gaa ccc att ttg aac tac ttg cgt cat gga cag ctc att gta aat 661
Phe Glu Pro Ile Leu Asn Tyr Leu Arg His Gly Gln Leu Ile Val Asn
145 150 155 160

gat ggc att aat tta ttg ggt gtg tta gaa gaa gca aga ttt ttt ggt 709
Asp Gly Ile Asn Leu Leu Gly Val Leu Glu Glu Ala Arg Phe Phe Gly
165 170 175

att gac tca ttg att gaa cac cta gaa gtg gca ata aag aat tct caa 757
Ile Asp Ser Leu Ile Glu His Leu Glu Val Ala Ile Lys Asn Ser Gln
180 185 190

cca ccg gag gat cat tca cca ata tcc cga aag gaa ttt gtc cga ttt 805

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Pro Pro Glu Asp His Ser Pro Ile Ser Arg Lys Glu Phe Val Arg Phe
        195                 200                 205

ttg cta gca act cca acc aag tca gaa ctg cga tgc cag ggt ttg aac      853
Leu Leu Ala Thr Pro Thr Lys Ser Glu Leu Arg Cys Gln Gly Leu Asn
    210                 215                 220

ttc agt ggt gct gat ctt tct cgt ttg gac ctt cga tac att aac ttc      901
Phe Ser Gly Ala Asp Leu Ser Arg Leu Asp Leu Arg Tyr Ile Asn Phe
225                 230                 235                 240

aaa atg gcc aat tta agc cgc tgt aat ctt gca cat gca aat ctt tgc      949
Lys Met Ala Asn Leu Ser Arg Cys Asn Leu Ala His Ala Asn Leu Cys
                245                 250                 255

tgt gca aat ctt gaa cga gct gat ctc tct gga tca gtg ctt gac tgt      997
Cys Ala Asn Leu Glu Arg Ala Asp Leu Ser Gly Ser Val Leu Asp Cys
            260                 265                 270

gcg aat ctc cag gga gtc aag atg ctc tgt tct aat gca gaa gga gca     1045
Ala Asn Leu Gln Gly Val Lys Met Leu Cys Ser Asn Ala Glu Gly Ala
        275                 280                 285

tcc ctg aaa ctg tgt aat ttt gag gat cct tct ggt ctt aaa gcc aat     1093
Ser Leu Lys Leu Cys Asn Phe Glu Asp Pro Ser Gly Leu Lys Ala Asn
    290                 295                 300

tta gaa ggt gct aat ctg aaa ggt gtg gat atg gaa gga agt cag atg     1141
Leu Glu Gly Ala Asn Leu Lys Gly Val Asp Met Glu Gly Ser Gln Met
305                 310                 315                 320

aca gga att aac ctg aga gtg gct acc tta aaa aat gca aag ttg aag     1189
Thr Gly Ile Asn Leu Arg Val Ala Thr Leu Lys Asn Ala Lys Leu Lys
                325                 330                 335

aac tgt aac ctc aga gga gca act ctg gca gga act gat tta gag aat     1237
Asn Cys Asn Leu Arg Gly Ala Thr Leu Ala Gly Thr Asp Leu Glu Asn
            340                 345                 350

tgt gat ctg tct ggg tgt gat ctt caa gaa gcc aac ctg aga ggg tcc     1285
Cys Asp Leu Ser Gly Cys Asp Leu Gln Glu Ala Asn Leu Arg Gly Ser
        355                 360                 365

aac gtg aag gga gct ata ttt gaa gag atg ctg aca cca cta cac atg     1333
Asn Val Lys Gly Ala Ile Phe Glu Glu Met Leu Thr Pro Leu His Met
    370                 375                 380

tca caa agt gtc aga t gagaatttta ggggctggag gaagatgtaa aagatgaaaa   1389
Ser Gln Ser Val Arg
385

tgttttcctt atcacttttc tttctccacc cactcagttg tctagaagaa ataacactgt   1449
aaggaaattt taaaaaaaaa catttagagg attatgcttg ttttgagtgg tgcataaggg   1509
aaaaaactga cttttttttcc atattctgat ttttaacaga aaagcactca tttaatagat  1569
gtagggaaac tagatattgc tgccttttga atggggtagg ggggtttacc tggttttatg   1629
accaggcata gtatctatta tatttgcttt taaataggca tgatgtggaa ataccatctt   1689
ggtttgagat gcatttgagg attttaattt atggaaagca caacatatgc aattatattt   1749
attgaattcc tagatgcagt atggatattt aaattgttaa aactttatga aaacttggaa   1809
aaggttgttc aggtttataa atagctttag tgatgcctcc cctctttaaa tacctgtcac   1869
accgtatgaa tatggtgaga tcagactccc taagactctt ttcaggttca tttttataat   1929
gtttactttt taggacagaa cagtagctaa attaaagtaa tatccagttc ttactgattg   1989
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agacagagtg gaaagaaaga catcattgta catcactgtc attccaaagg tacagtgtaa 2049
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atttcattct aggcaagttc cactcaacac cagatcaagc aattctatct atttacacta 2169
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accaaggtgc atcattaata ttcatttaat tcaaatacca aatagtttac atagggccag 2289
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aaaaaaaaaa aaaaa 3204

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<213> H. sapiens

<400> 27
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Val Val Ala Val Tyr Gly Thr Leu Ser Asp Leu Leu Ser Val Ala Ser
20 25 30
Ser Lys Leu Gly Ile Lys Ala Thr Ser Val Tyr Asn Gly Lys Gly Gly
35 40 45
Leu Ile Asp Asp Ile Ala Leu Ile Arg Asp Asp Asp Val Leu Phe Val
50 55 60
Cys Glu Gly Glu Pro Phe Ile Asp Pro Gln Thr Asp Ser Lys Pro Pro
65 70 75 80
Glu Gly Leu Leu Gly Phe His Thr Asp Trp Leu Thr Leu Asn Val Gly
85 90 95
Gly Arg Tyr Phe Thr Thr Thr Arg Ser Thr Leu Val Asn Lys Glu Pro
100 105 110
Asp Ser Met Leu Ala His Met Phe Lys Asp Lys Gly Val Trp Gly Asn
115 120 125
Lys Gln Asp His Arg Gly Ala Phe Leu Ile Asp Arg Ser Pro Glu Tyr
130 135 140
Phe Glu Pro Ile Leu Asn Tyr Leu Arg His Gly Gln Leu Ile Val Asn
145 150 155 160
Asp Gly Ile Asn Leu Leu Gly Val Leu Glu Glu Ala Arg Phe Phe Gly
165 170 175
Ile Asp Ser Leu Ile Glu His Leu Glu Val Ala Ile Lys Asn Ser Gln
180 185 190
Pro Pro Glu Asp His Ser Pro Ile Ser Arg Lys Glu Phe Val Arg Phe
195 200 205
Leu Leu Ala Thr Pro Thr Lys Ser Glu Leu Arg Cys Gln Gly Leu Asn
210 215 220
Phe Ser Gly Ala Asp Leu Ser Arg Leu Asp Leu Arg Tyr Ile Asn Phe
225 230 235 240
Lys Met Ala Asn Leu Ser Arg Cys Asn Leu Ala His Ala Asn Leu Cys
245 250 255
Cys Ala Asn Leu Glu Arg Ala Asp Leu Ser Gly Ser Val Leu Asp Cys

260 265 270
Ala Asn Leu Gln Gly Val Lys Met Leu Cys Ser Asn Ala Glu Gly Ala
275 280 285
Ser Leu Lys Leu Cys Asn Phe Glu Asp Pro Ser Gly Leu Lys Ala Asn
290 295 300
Leu Glu Gly Ala Asn Leu Lys Gly Val Asp Met Glu Gly Ser Gln Met
305 310 315 320
Thr Gly Ile Asn Leu Arg Val Ala Thr Leu Lys Asn Ala Lys Leu Lys
325 330 335
Asn Cys Asn Leu Arg Gly Ala Thr Leu Ala Gly Thr Asp Leu Glu Asn
340 345 350
Cys Asp Leu Ser Gly Cys Asp Leu Gln Glu Ala Asn Leu Arg Gly Ser
355 360 365
Asn Val Lys Gly Ala Ile Phe Glu Glu Met Leu Thr Pro Leu His Met
370 375 380
Ser Gln Ser Val Arg
385

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<223> K+Hnov44, splice 1

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ttctaatggc tgcagctgcg ctgggggctg ggggctcccg ctgggactcc acttccgtgg 180
atgtctaagc ttcacctttc ttgcgcccgc aggggcatga ctcaggtgaa agggagccat 240
tttctcagac ccctggcctc atgcagccct tcagcatccc cgtgcaaatc acacttcagg 300
gcagccggag gcgccagggg aggacagcct ttcctgcctc agggaagaag agagagacag 360
actacagtga tggagaccca ctagatgtgc acaagaggct gccatccagt gctggagagg 420
accgagccgt g atg ctg ggg ttt gcc atg atg ggc ttc tca gtc cta atg 470
Met Leu Gly Phe Ala Met Met Gly Phe Ser Val Leu Met
1 5 10

ttc ttc ttg ctc gga aca acc att cta aag cct ttt atg ctc agc att 518
Phe Phe Leu Leu Gly Thr Thr Ile Leu Lys Pro Phe Met Leu Ser Ile
15 20 25

cag aga gaa gaa tcg acc tgc act gcc atc cac aca gat atc atg gac 566
Gln Arg Glu Glu Ser Thr Cys Thr Ala Ile His Thr Asp Ile Met Asp
30 35 40 45

gac tgg ctg gac tgt gcc ttc acc tgt ggt gtg cac tgc cac ggt cag 614
Asp Trp Leu Asp Cys Ala Phe Thr Cys Gly Val His Cys His Gly Gln
50 55 60

ggg aag tac ccg tgt ctt cag gtg ttt gtg aac ctc agc cat cca ggt 662
Gly Lys Tyr Pro Cys Leu Gln Val Phe Val Asn Leu Ser His Pro Gly
65 70 75

cag aaa gct ctc cta cat tat aat gaa gag gct gtc cag ata aat ccc 710
Gln Lys Ala Leu Leu His Tyr Asn Glu Glu Ala Val Gln Ile Asn Pro
80 85 90

aag tgc ttt tac aca cct aag tgc cac caa gat aga aat gat ttg ctc 758

Lys Cys Phe Tyr Thr Pro Lys Cys His Gln Asp Arg Asn Asp Leu Leu
95 100 105

aac agt gct ctg gac ata aaa gaa ttc ttc gat cac aaa aat gga act 806
Asn Ser Ala Leu Asp Ile Lys Glu Phe Phe Asp His Lys Asn Gly Thr
110 115 120 125

ccc ttt tca tgc ttc tac agt cca gcc agc caa tct gaa gat gtc att 854
Pro Phe Ser Cys Phe Tyr Ser Pro Ala Ser Gln Ser Glu Asp Val Ile
130 135 140

ctt ata aaa aag tat gac caa atg gct atc ttc cac tgt tta ttt tgg 902
Leu Ile Lys Lys Tyr Asp Gln Met Ala Ile Phe His Cys Leu Phe Trp
145 150 155

cct tca ctg act ctg cta ggt ggt gcc ctg att gtt ggc atg gtg aga 950
Pro Ser Leu Thr Leu Leu Gly Gly Ala Leu Ile Val Gly Met Val Arg
160 165 170

tta aca caa cac ctg tcc tta ctg tgt gaa aaa tat agc act gta gtc 998
Leu Thr Gln His Leu Ser Leu Leu Cys Glu Lys Tyr Ser Thr Val Val
175 180 185

aga gat gag gta ggt gga aaa gta cct tat ata gaa cag cat cag ttc 1046
Arg Asp Glu Val Gly Gly Lys Val Pro Tyr Ile Glu Gln His Gln Phe
190 195 200 205

aaa ctg tgc att atg agg agg agc aaa gga aga gca gag aaa tct t 1092
Lys Leu Cys Ile Met Arg Arg Ser Lys Gly Arg Ala Glu Lys Ser
210 215 220

aagacggtgg ccaaattaaa gtgctggcct tcagatgtct gtgatttctg caactgagga 1152
cctaattatg cctgtctgca aactaataat gtaaaaggta ataattaaag tatcatattt 1212
tcatgtggga aaaaaaaaaa aaaaaaaaaa aaaa 1246

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aggcaggcgg caggcgtggt gcacaagaag tctgagtgtg aggggctctt ttctctccac 180
tgccaatgac agcctttcct gcctcaggga agaagagaga gacagactac agtgatggag 240
acccactaga tgtgcacaag aggctgccat ccagtgctgg agaggaccga gccgtg atg 299
Met
1

ctg ggg ttt gcc atg atg ggc ttc tca gtc cta atg ttc ttc ttg ctc 347
Leu Gly Phe Ala Met Met Gly Phe Ser Val Leu Met Phe Phe Leu Leu
5 10 15

gga aca acc att cta aag cct ttt atg ctc agc att cag aga gaa gaa 395
Gly Thr Thr Ile Leu Lys Pro Phe Met Leu Ser Ile Gln Arg Glu Glu
20 25 30

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tcg acc tgc act gcc atc cac aca gat atc atg gac gac tgg ctg gac      443
Ser Thr Cys Thr Ala Ile His Thr Asp Ile Met Asp Asp Trp Leu Asp
     35                  40                  45

tgt gcc ttc acc tgt ggt gtg cac tgc cac ggt cag ggg aag tac ccg      491
Cys Ala Phe Thr Cys Gly Val His Cys His Gly Gln Gly Lys Tyr Pro
 50                  55                  60                  65

tgt ctt cag gtg ttt gtg aac ctc agc cat cca ggt cag aaa gct ctc      539
Cys Leu Gln Val Phe Val Asn Leu Ser His Pro Gly Gln Lys Ala Leu
                 70                  75                  80

cta cat tat aat gaa gag gct gtc cag ata aat ccc aag tgc ttt tac      587
Leu His Tyr Asn Glu Glu Ala Val Gln Ile Asn Pro Lys Cys Phe Tyr
             85                  90                  95

aca cct aag tgc cac caa gat aga aat gat ttg ctc aac agt gct ctg      635
Thr Pro Lys Cys His Gln Asp Arg Asn Asp Leu Leu Asn Ser Ala Leu
        100                 105                 110

gac ata aaa gaa ttc ttc gat cac aaa aat gga act ccc ttt tca tgc      683
Asp Ile Lys Glu Phe Phe Asp His Lys Asn Gly Thr Pro Phe Ser Cys
    115                 120                 125

ttc tac agt cca gcc agc caa tct gaa gat gtc att ctt ata aaa aag      731
Phe Tyr Ser Pro Ala Ser Gln Ser Glu Asp Val Ile Leu Ile Lys Lys
130                 135                 140                 145

tat gac caa atg gct atc ttc cac tgt tta ttt tgg cct tca ctg act      779
Tyr Asp Gln Met Ala Ile Phe His Cys Leu Phe Trp Pro Ser Leu Thr
                150                 155                 160

ctg cta ggt ggt gcc ctg att gtt ggc atg gtg aga tta aca caa cac      827
Leu Leu Gly Gly Ala Leu Ile Val Gly Met Val Arg Leu Thr Gln His
            165                 170                 175

ctg tcc tta ctg tgt gaa aaa tat agc act gta gtc aga gat gag gta      875
Leu Ser Leu Leu Cys Glu Lys Tyr Ser Thr Val Val Arg Asp Glu Val
        180                 185                 190

ggt gga aaa gta cct tat ata gaa cag cat cag ttc aaa ctg tgc att      923
Gly Gly Lys Val Pro Tyr Ile Glu Gln His Gln Phe Lys Leu Cys Ile
    195                 200                 205

atg agg agg agc aaa gga aga gca gag aaa tct t aagacggtgg             967
Met Arg Arg Ser Lys Gly Arg Ala Glu Lys Ser
210                 215                 220

ccaaattaaa gtgctggcct tcagatgtct gtgatttctg caactgagga cctaattatg   1027
cctgtctgca aactaataat gtaaaggta ataattaaag tatcatattt tcatgtggga    1087
aaaaaaaaaa aaaaaaaaaa aaaa                                          1111

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Leu Gly Thr Thr Ile Leu Lys Pro Phe Met Leu Ser Ile Gln Arg Glu
            20                  25                  30
Glu Ser Thr Cys Thr Ala Ile His Thr Asp Ile Met Asp Asp Trp Leu
        35                  40                  45
Asp Cys Ala Phe Thr Cys Gly Val His Cys His Gly Gln Gly Lys Tyr
    50                  55                  60
Pro Cys Leu Gln Val Phe Val Asn Leu Ser His Pro Gly Gln Lys Ala
65                  70                  75                  80
Leu Leu His Tyr Asn Glu Glu Ala Val Gln Ile Asn Pro Lys Cys Phe
                85                  90                  95
Tyr Thr Pro Lys Cys His Gln Asp Arg Asn Asp Leu Leu Asn Ser Ala
            100                 105                 110
Leu Asp Ile Lys Glu Phe Phe Asp His Lys Asn Gly Thr Pro Phe Ser
        115                 120                 125
Cys Phe Tyr Ser Pro Ala Ser Gln Ser Glu Asp Val Ile Leu Ile Lys
    130                 135                 140
Lys Tyr Asp Gln Met Ala Ile Phe His Cys Leu Phe Trp Pro Ser Leu
145                 150                 155                 160
Thr Leu Leu Gly Gly Ala Leu Ile Val Gly Met Val Arg Leu Thr Gln
                165                 170                 175
His Leu Ser Leu Leu Cys Glu Lys Tyr Ser Thr Val Val Arg Asp Glu
            180                 185                 190
Val Gly Gly Lys Val Pro Tyr Ile Glu Gln His Gln Phe Lys Leu Cys
        195                 200                 205
Ile Met Arg Arg Ser Lys Gly Arg Ala Glu Lys Ser
    210                 215                 220
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<400> 32
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<210> 33
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<400> 33
tgacatcact ggatgaactt ga 22

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<400> 34
tgcctgcaaa gtttgaacat 20

<210> 35
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tgacatcact ggatgaactt ga 22

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<400> 36
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<210> 37
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<400> 37
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atctttgtca gccaccagct 20

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<210> 57
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<212> DNA
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<400> 58
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<210> 59
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<210> 61
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<400> 61
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<400> 66
tttctcttct ccattgaagt tcaagttacc attgggtttg gagggag 47

<210> 67
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<400> 68
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<210> 69
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<400> 69
Trp Trp Ala Val Val Thr Met Thr Thr Leu Gly Tyr Gly Asp Met
1 5 10 15

<210> 70
<211> 15
<212> PRT
<213> Artificial Sequence

<400> 70
Trp Trp Gly Val Val Thr Val Thr Thr Ile Gly Tyr Gly Asp Lys
1 5 10 15

<210> 71
<211> 15
<212> PRT
<213> Artificial Sequence

<400> 71
Trp Trp Ala Val Val Thr Met Thr Thr Val Gly Tyr Gly Asp Met
1 5 10 15

<210> 72

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<211> 15
<212> PRT
<213> Artificial Sequence

<400> 72
Phe Leu Phe Ser Ile Glu Val Gln Val Thr Ile Gly Phe Gly Gly
 1               5                   10                  15

<210> 73
<211> 15
<212> PRT
<213> Artificial Sequence

<400> 73
Phe Leu Phe Ser Leu Glu Ser Gln Thr Thr Ile Gly Tyr Gly Val
 1               5                   10                  15

<210> 74
<211> 15
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<213> Artificial Sequence

<400> 74
Phe Leu Phe Ser Ile Glu Thr Glu Thr Thr Ile Gly Tyr Gly Tyr
 1               5                   10                  15

<210> 75
<211> 15
<212> PRT
<213> Artificial Sequence

<400> 75
Phe Leu Phe Ser Ile Glu Thr Gln Thr Thr Ile Gly Tyr Gly Phe
 1               5                   10                  15

<210> 76
<211> 15
<212> PRT
<213> Artificial Sequence

<400> 76
Phe Leu Phe Ser Val Glu Thr Gln Thr Thr Ile Gly Tyr Gly Phe
 1               5                   10                  15

<210> 77
<211> 15
<212> PRT
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<400> 77
Phe Leu Phe Ser Leu Glu Ser Gln Thr Thr Ile Gly Tyr Gly Phe
 1               5                   10                  15

<210> 78
<211> 15
<212> PRT
<213> Artificial Sequence

<400> 78
Phe Leu Phe Ser Ile Glu Thr Glu Thr Thr Ile Gly Tyr Gly Phe
 1               5                   10                  15
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<210> 79
<211> 16
<212> PRT
<213> Artificial Sequence

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Leu Arg Ala Glu Leu Glu Thr Leu Arg Ala Gln Leu Leu Gln Arg Ser
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ccg tgt gtg gct gcc ccc gcc ctg gac gcc ttc gtg gag cga gtg ctg 310
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Arg Val Leu Ala Ala Gly Arg Leu Gly Arg Val Val Leu Ala Asn Ala
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Ser Gly Ser Ala Asn Ala Ser Asp Pro Ala Trp Asp Phe Ala Ser Ala
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Leu Phe Phe Ala Ser Thr Leu Ile Thr Thr Val Gly Tyr Gly Tyr Thr
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Thr Pro Leu Thr Asp Ala Gly Lys Ala Phe Ser Ile Ala Phe Ala Leu
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Trp Gly Trp Asp Pro Arg Arg Ala Ala Cys Trp His Leu Val Ala Leu
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Leu Gly Val Val Val Thr Val Cys Phe Leu Val Pro Ala Val Ile Phe
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Lys Gln Thr Phe Ile Ser Gln His Ser Cys Val Asn Ser Thr Glu Leu
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cag cta ggc acc ata ttt gga aaa gga att gcc aaa gtg gaa gat acg      634
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Val Ile Gln Lys Gln Thr Phe Ile Ser Gln His Ser Cys Val Asn Ser
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Glu Asp Thr Phe Ile Lys Trp Asn Val Ser Gln Thr Lys Ile Arg Ile
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/03826

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07H 21/04; C07K 14/705; C12N 15/09, 15/63; C12Q 1/68
US CL : 636/23.1, 24.3; 435/7.2, 69.1, 320.1; 530/350
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 636/23.1, 24.3; 435/7.2, 69.1, 320.1; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	PARTISETI, M. et al. Cloning and Characteization of a Novel Human Inward Rectifying Potassium Channel Predominantly Expressed in Small Intestine. FEBS Lett. 1998, Vol. 434, pages 171-176, see entire document.	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
28 MAY 1999

Date of mailing of the international search report
07 JUL 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
NIRMAL S. BASI
D. Lawrence Jer
Telephone No. (703) 308-0196

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, MEDLINE, JAPIO, BIOSIS, SCISEARCH, WPIDS, GENEMBL, NGENSEQ 34, EST, A-GENESEQ 32, PIR 58, SWISS-PROT 35, SPTREMBL 16.
search terms: potassium channel, K+hnov

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:2, the nucleic acid having the sequence of SEQ ID NO:1, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:2 and K+Hnov protein of SEQ ID NO:2.
Group II, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:4, the nucleic acid having the sequence of SEQ ID NO:3, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:4 and K+Hnov protein of SEQ ID NO:4.
Group III, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:6, the nucleic acid having the sequence of SEQ ID NO:5, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:6 and K+Hnov protein of SEQ ID NO:6.
Group IV, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:8, the nucleic acid having the sequence of SEQ ID NO:7, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:8 and K+Hnov protein of SEQ ID NO:8.
Group V, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:10, the nucleic acid having the sequence of SEQ ID NO:9, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:10 and K+Hnov protein of SEQ ID NO:10.
Group VI, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:12, the nucleic acid having the sequence of SEQ ID NO:11, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:12 and K+Hnov protein of SEQ ID NO:12.
Group VII, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:14, the nucleic acid having the sequence of SEQ ID NO:13, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:14 and K+Hnov protein of SEQ ID NO:14.
Group VIII, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:16, the nucleic acid having the sequence of SEQ ID NO:15, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:16 and K+Hnov protein of SEQ ID NO:16.
Group IX, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:18, the nucleic acid having the sequence of SEQ ID NO:17, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:18 and K+Hnov protein of SEQ ID NO:18.
Group X, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:20, the nucleic acid having the sequence of SEQ ID NO:19, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:20 and K+Hnov protein of SEQ ID NO:20.
Group XI, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:25, the nucleic acid having the sequence of SEQ ID NO:21-25, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:25 and K+Hnov protein of SEQ ID NO:25.
Group XII, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:27, the nucleic acid having the sequence of SEQ ID NO:26, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing

K+Hnov protein of SEQ ID NO:27 and K+Hnov protein of SEQ ID NO:27.
Group XIII, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:30, the nucleic acid having the sequence of SEQ ID NO:28-29, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:30 and K+Hnov protein of SEQ ID NO:30.
Group XIV, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:81, the nucleic acid having the sequence of SEQ ID NO:80, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:81 and K+Hnov protein of SEQ ID NO:81.
Group XV, claim(s)1-9, drawn to nucleic acids encoding K+Hnov protein having the amino acid sequence of SEQ ID NO:83, the nucleic acid having the sequence of SEQ ID NO:82, nucleic acids hybridizing to said nucleic acids, expression cassette comprising said nucleic acids, cell comprising said expression cassette, method for producing K+Hnov protein of SEQ ID NO:83 and K+Hnov protein of SEQ ID NO:83.
Group XVI, claim(s)10, drawn to monoclonal antibody that binds to K+Hnov.
Group XVII, claim(s)11-14, drawn to non-human transgenic animal model for K+Hnov.

The inventions listed as Groups I-XVII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I is directed to nucleic acid (SEQ ID NO:1) encoding the K+Hnov protein of SEQ ID NO:2, nucleic acids hybridizing to said nucleic acid, expression cassette comprising said nucleic acid, cell comprising said cassette, method of producing the K+Hnov of SEQ ID NO:2 and the protein of SEQ ID NO:2. The special technical feature is the disclosed nucleic acid of SEQ ID NO:1 encoding the K+Hnov protein of SEQ ID NO:2. The nucleic acids, proteins, antibody and transgenic animal model of Groups II-XVII do not share the special technical feature of Group I wherein the products of said Groups are structurally and functionally different. As shown in Table 1, pages 8-9, the H+Nov proteins of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 27, 30, 81 and 83 are all structurally and functionally different, the nucleic acids encoding said proteins having different chromosome positions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/03826

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
   1-9, SEQ ID NO:1 and 2

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.